L E C T U R E

Synaptic plasticity and the neurobiology of learning and memory

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Abstract. Learning and memory are fundamental higher brain functions that allow the individual to adapt to the environment, to build up his own history as a unique creature, to widen the personal cultural background and, ultimately, the population culture. In this review, we will briefly examine the cellular and molecular mechanisms that contribute to the various forms of memory that include short- and long-term memory as well as unconscious and conscious memory. Although in mammals various brain areas participate in distinct forms of memory, the molecular and cellular mechanisms of very simple to complex forms of learning and memory are extremely conserved across evolution from molluscs to man and among various forms of memory and consist in short-to-long lived rearrangements in synaptic efficiency and in the structure of neuronal networks. (www.actabiomedica.it)

Key words: Neurotransmitter release, synaptic strength, protein phosphorylation, short-term plasticity, long-term plasticity, implicit memory, declarative memory

Introduction

Neurons are specialized for communication and information processing. Neurons are highly polarized cells composed of distinct functional compartments, namely: (i) a receiving domain represented by dendrites and the cell body that receives information from other neurons at numerous (about 1,000 in the average) synaptic contacts; (ii) an integration domain, represented by the initial segment of the axon (the most excitable part of the neuron) that integrates all the received information within time and space and takes the final decision of whether or not generate an action potential; (iii) a cable domain, the axon, specialized for the rapid transfer of the nerve impulse and (iv) a transmission domain, the nerve terminal, that is specialized in transducing the all-or-none nerve impulse in a highly regulated exocytotic release of a chemical messenger (neurotransmitter) for which specific receptors exist on the postsynaptic neuron (1).

The specific areas of contact between neurons were named synapses (from the Greek term "tighten together") by the British physiologist Charles S. Sherrington. In chemical synapses, which account for most if not all mammalian synapses, neurotransmitters are stored in synaptic vesicles within the presynaptic terminal and are released by a process of regulated exocytosis. Neurotransmitter release preferentially occurs at the active zone, a highly specialized area of the presynaptic membrane, and is triggered by depolarization that promotes Ca^{2+} influx through voltage-dependent Ca^{2+} channels (Fig. 1). Once secreted, the neurotransmitter rapidly diffuses within the narrow synaptic cleft to reach postsynaptic receptors that bind and transduce it into an electrical and/or metabolic response of the postsynaptic neuron. While neurons can rapidly transmit over long distances only a digital stereotyped signal (the action potential) that cannot be modulated in amplitude, but only in frequency, at the synapse a digital-to-analogic process occurs that
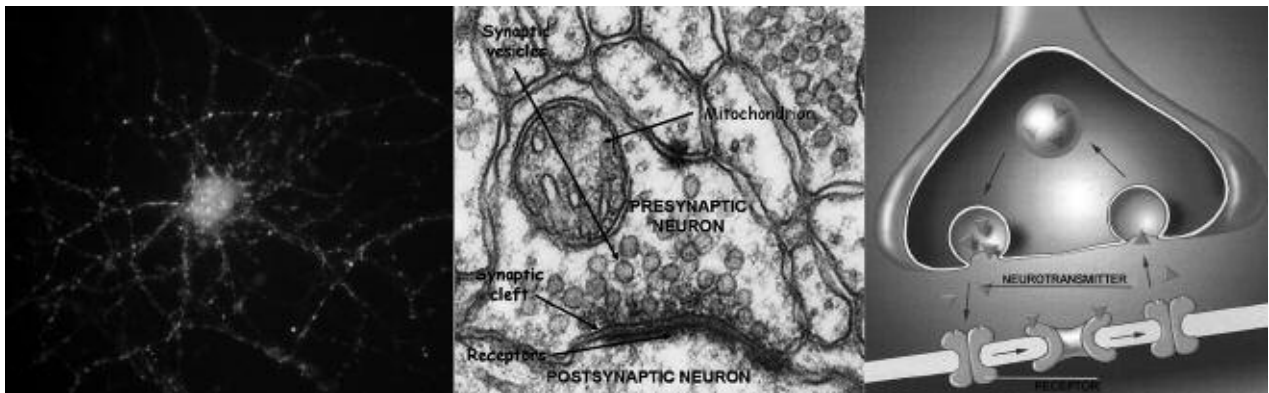
Figure 1. Synaptic connections among neurons. *Left panel:* a large hippocampal neuron in culture receiving multiple synaptic inputs labelled for the presynaptic protein synaptophysin. *Middle and right panel:* ultrastructure and schematics of a chemical synapse. The neurotransmitter is stored in synaptic vesicles which undergo an activity-dependent exo-endocytotic cycle and, once released into the synaptic cleft, stimulates adjacent postsynaptic receptors

makes possible that an identical signal can be transmitted across the synaptic cleft in a highly modulatable fashion (2, 3).

The efficiency of information transfer through the synapse, called "synaptic strength" depends on the complexity of the signal transduction processes including an electrical-to-chemical transduction at the presynaptic level followed by a chemical-to-electrical/metabolic transduction at the postsynaptic level. In other words, an action potential can promote exocytosis of a variable number of synaptic vesicles, each containing a highly reproducible number of neurotransmitter molecules (the neurotransmitter "*quantum*") and neurotransmitter molecules can be bound by a variable number and type of postsynaptic receptors. Thus, synaptic strength can be regulated by a variety of pre- and post-synaptic events and depends on three factors that can be determined experimentally, namely (i) the number of active release sites "n", corresponding to the number of synaptic vesicles ready for release at the active zone; (ii) the probability "p" of each vesicle to undergo fusion at the arrival of the action potential; and (iii) the quantum content "q" that depends on both the number of neurotransmitter molecules per vesicle (generally a very constant value) and the number of stimulated receptors on the postsynaptic side. These three parameters are very sensitive to the previous history of the neuron (e.g., previous patterns of stimulation), as well as to intracellular messengers and protein phosphorylation processes at both pre- and post-synaptic sides (1-3).

Synaptic plasticity and the cellular bases of memory

The major and most distinctive feature of the nervous system is the astonishing ability to adapt to the environment and to improve its performance over time and experience. This peculiar property, collectively named "plasticity", has been precisely defined at the end of the XIX century by Santiago Ramon y Cajal as "*the property by virtue of which sustained functional changes occur in particular neuronal systems following the administration of appropriate environmental stimuli or the combination of different stimuli*". Since the neural changes evoked by the stimuli can persist for very long times, virtually for the whole life of the individual, it seems clear that neural plasticity represents the basis of the higher brain functions such as learning and memory or, conversely, that the built-in property of neural plasticity allows experience to shape both functionally and structurally the nervous system. The latter aspect, predicted in the III century BC by the Greek philosopher Epicurus who wrote that "*it's because something of the external objects penetrates in ourselves that we can identify shapes and think*", is also a fundamental aspect of neural development and maturation. It is known that neurons are generated in great

excess and only some of them, selected on the basis of the size and activity of the innervated territories, survive, while the others undergo programmed cell death. Selected neurons then grow processes and contact target neurons that are recognized on the basis of a mosaic of secreted and membrane-exposed signals whose expression is genetically determined. Thus, the first assembly or neuronal networks is driven by genetic factors, i.e. by the size of the physiological targets and the expression of chemotactic and/or cell adhesion "recognition" proteins whose genes are specifically transcribed and translated by the various neuronal populations (1).

After this first gene-driven developmental period, neuronal circuits are continuously modified and shaped by experience (epigenetic development): synaptic connections that are scarcely used become weaker and weaker and eventually disappear, whereas synapses that are heavily used become stronger and stronger and eventually increase in number. As mentioned above, synaptic strength can be finely tuned over a short or even a long time scale by a combination of factors including previous activity of the network, generation of second messengers, functional changes in pre- and post-synaptic proteins as well as regulation of the expression of genes implicated in growth, survival and synaptic transmission. This results in changes in the efficiency of synaptic transmission, that can last from fraction of seconds to minutes in case of short-term synaptic plasticity (including paired-pulse facilitation or depression, augmentation, depression, post-tetanic potentiation) to hours, days and months in case of long-term synaptic plasticity (long-term potentiation, long-term depression). These changes deeply affect the processing carried out between input and output information and, ultimately, shape the flow of information within the neural network (Fig. 2). A similar hypothesis was also formulated by Sigmund Freud, who was convinced that "*all the psychological matters that we are progressively formulating, will have to rely, one day, on an organic substrate*". Thus, the physical structure of memory traces could be an activity-dependent synaptic plasticity.

Up to few years ago, the theories of memory did not go beyond a description by analogy (Fig. 3). Such way of describing complex biological problems is
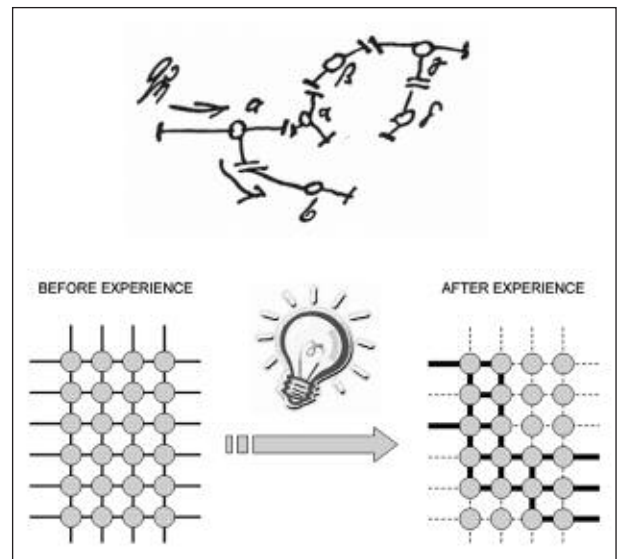

Figure 2. Synaptic plasticity and memory. *Upper panel:* Sigmund Freud's drawing putting forward the possibility of a change in the gain of synaptic connections in a neuronal network as the basis of learning and memory. *Lower panel:* an experience can modify pre-structured neuronal networks by changing the efficiency of transmission in selective synaptic connections, thereby modifying the flow of information within the network

clearly limited by the current stage of technological progress. Virtually all historical models of memory are based on the instruments that humans have used to store information, from the Descartes model of a canvas in which memory traces are printed with an array of needles, to the "industrial revolution" model of a general archive inside the brain to the computer model of memory cells (4).

Two major types of memory exist, one for skills and one for knowledge. The first one refers to information storage to perform various reflexive or perceptual tasks is also referred to as non-declarative or implicit memory because it is recalled unconsciously. When we use implicit memory, we act automatically and we are not aware of being recalling memory traces. Implicit memory is a heterogeneous collection of memory functions and types of learned behaviours such as reflexive learning (sensitization, habituation), classical conditioning, fear conditioning, procedural memory (for skills and habits) and priming (the recall of words or objects from a previous unconscious exposure to them).
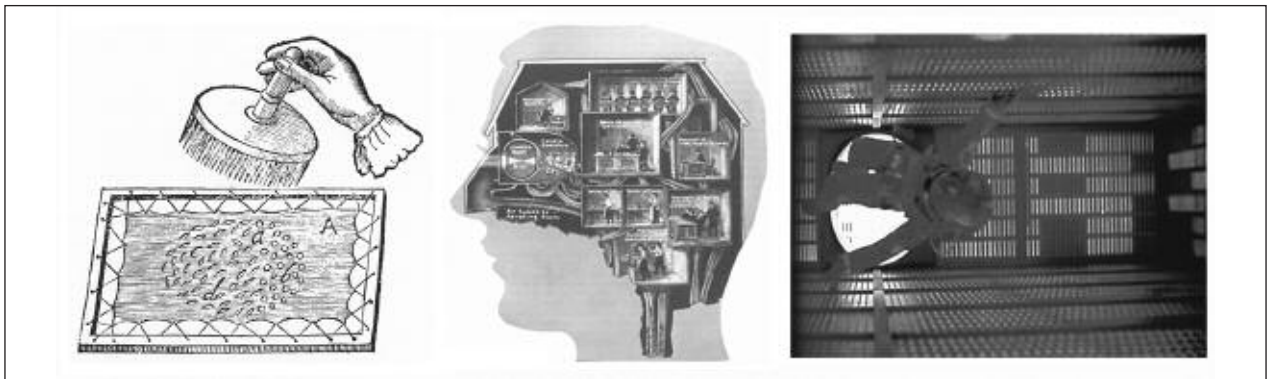
Figure 3. Historical models of memory storage. *Left panel:* René Descartes' model of memory seen as distributed pores in the ventricular wall (holes in a canvas) printed by experience (array of needles) and perfused with a life spirit ("*Traité de l'homme*", 1664). *Middle panel:* "industrial revolution" model (1930): the site where memories are stored in the brain is represented as a general archive of an industry. *Right panel*: computer model of memory from Stanley Kubrik's "*2001: a space odissey*" (1968). Memory traces are stored in memory pack in the HAL9000 mother board. With permission

The second form of memory, called declarative or explicit memory because it is recalled by a deliberate and conscious effort, concerns factual knowledge of persons, things, notions and places. Declarative memory can be further classified as episodic or autobiographic memory and semantic memory. Episodic memory allows us to remember personal events and experience and, being a link between what we are and what we have been, gives us the sense of our individuality. On the other hand, semantic memory is a sort of public memory for facts and notions, be they general or autobiographical (Fig. 4). Often, over time, autobiographical memory shades into semantic memory so that the experience of an event is remembered as the simple occurrence of such event (1, 5).

Neuropsychological studies on neurological patients, mainly pioneered by Brenda Millner with the famous H.M. case, have shown that the multiple me-
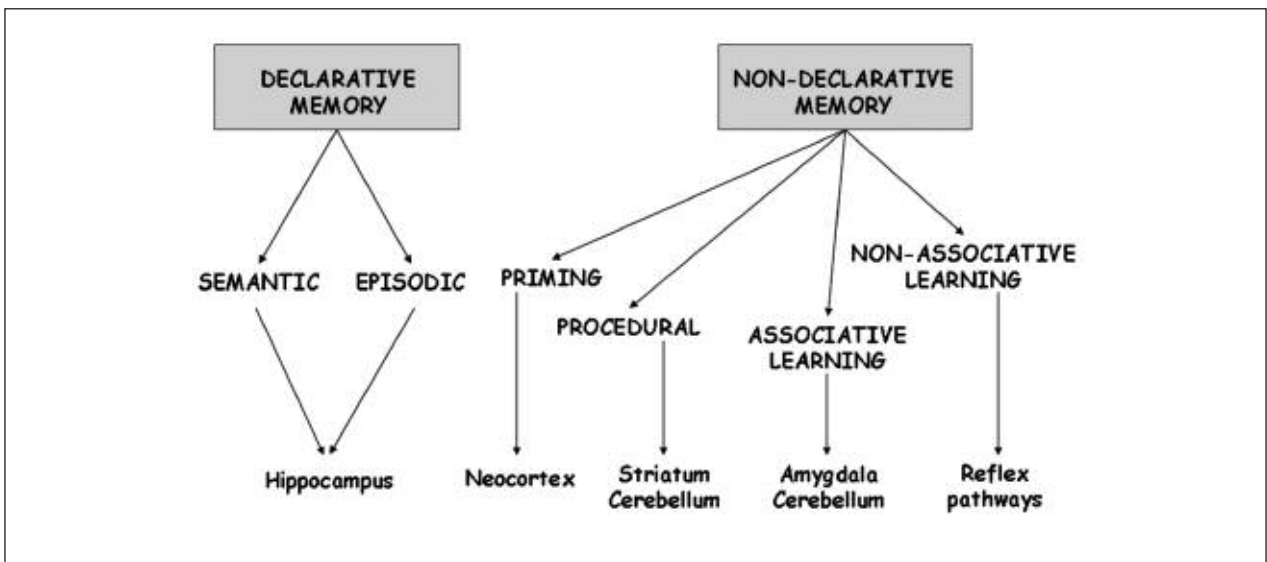

Figure 4. Different forms of learning and memory. Declarative or explicit memory can be further classified as semantic or episodic (autobiographic) memory is integrated in the hippocampus. Non-declarative or implicit memory is represented by a heterogeneous group of unconscious learning paradigms that are integrated by distinct brain areas. For further details, see text

mory systems involve distinct brain areas and exhibit distinctive features. Thus, explicit memory needs an intact medial temporal lobe (hippocampus), while implicit memory systems are integrated at various levels in the central nervous system including reflex pathways, striatum, cerebellum, amygdala and neocortex (Fig. 4). Moreover, the kinetics of the learning phase, consolidation and recall of memories are quite different. Implicit memory, such as learning to ride a bike, takes time and many attempts to build up, while explicit memory, such as learning a page of history or a telephone number, is more immediate and implies a smaller effort. However, while explicit memory fades relatively rapidly in the absence of recall and refreshing, implicit memory is much more robust and may last for all our life even in the absence of further practice (4, 5).

From short- to long-term memories: memory consolidation, forgetfulness and recall

Learning induces cellular and molecular changes that facilitate or impair communication among neurons and are fundamental for memory storage. If learning brings about changes in "synaptic strength" within neuronal circuits, the persistence of these changes represents the way memories are stored. Short-term memory is believed to involve only functional changes in pre-existing neuronal networks mediated by a fine tuning of multiple intracellular signal transductions systems. These short-lived changes can undergo either of two processes: either fade out with time (forgetfulness) or be reinforced and transformed into long-term memory by a process called memory consolidation (Fig. 5). Forgetfulness is at least as important as consolidation. Since a minimal part of what we perceive is useful, the brain needs a mechanism to prevent itself from being burdened by negligible information. To be consolidated, functional changes have to be followed by gene transcription and protein synthesis that produce permanent phenotypic changes in the neuron associated with structural rearrangements in neuronal networks. Thus, consolidation of memories is abolished by mRNA and protein synthesis inhibitors. Consolidation is not a high fidelity pro-
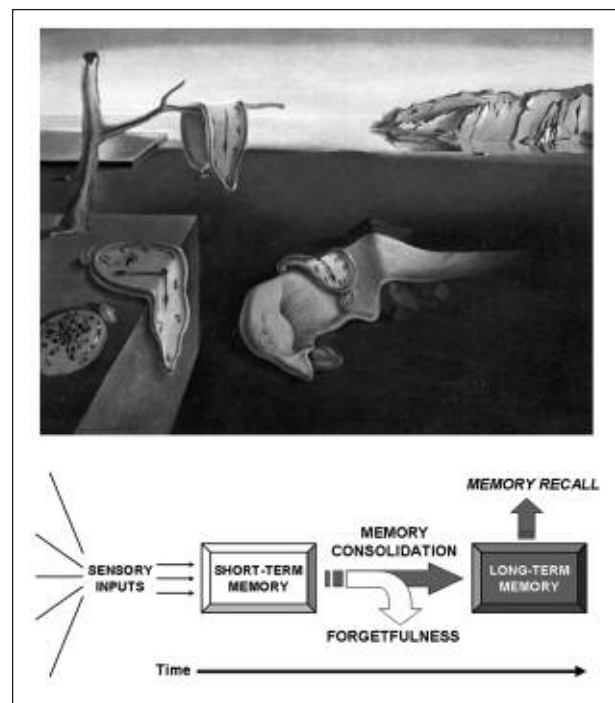

Figure 5. Memory consolidation, forgetfulness and recall. *Upper panel:* Salvador Dalì's "*The persistence of memory*" (1931; Museum of Modern Art, New York), with permission. *Lower panel:* time-dependent memory processes. Sensory inputs generate short-term memories that undergo a specific selection process. Only a small percentage of these memories are consolidated into long-term memories and can be retrieved later on, while most short-term memories are forgotten

cess: stored memories gradually change and fade with time and only the most relevant and useful aspects are retained over time (5, 6).

The processes involved in short-term memory include: (i) changes in the excitation-secretion coupling at the presynaptic level promoted by changes in channel conductances due to phosphorylation and Ca^{2+} influx; (ii) Ca^{2+} influx at the postsynaptic level through NMDA glutamate receptors by Ca^{2+}/calmodulin kinases, protein kinase C and tyrosine kinases promoting phosphorylation of neurotransmitter receptors and generation of retrograde messengers (such as nitric oxide and arachidonic acid) that reach the presynaptic terminal and increase neurotransmitter release in response to action potentials. The activation of the molecules involved in these signalling pathways can last for minutes and thereby represent a sort of short-term "molecular memory" (7-9). Notably, all reactions mediated by

phosphorylation typically have half-lives that depend on the kinetics of dephosphorylation by protein phosphatases. A very important role in the establishment of short-term memories is played by the balance between Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), a key enzyme in synaptic plasticity at both pre- and post-synaptic levels, and protein phosphatase 1 (PP1). Upon Ca^{2+} influx during training, CaMKII undergoes an autophosphorylation reaction that transforms it into a constitutively activated kinase. The "switched-on" CaMKII, however, is returned to the resting state by PP1 that thereby has an inhibitory effect on learning (6,7,10). Thus, the antagonistic interactions between CaMKII and PP1 represent a push-pull system that plays a fundamental role during learning as well as in the delicate balance between maintaining and forgetting stored memories (Fig. 6).

These purely functional changes cannot survive for long times in the absence of a structural rearrangement of the neurons participating in the modulated synapse. The sustained activation of the same pathways promotes memory consolidation by affec-

ting the gene transcription and translation. Sustained stimulation leads to persistent activation of the protein kinase A (PKA) and MAP kinase Erk (MAPK) pathways. In turn, PKA phosphorylates and activates the transcriptional activator CREB1a, whereas MAPK phosphorylates and inactivates the transcriptional repressor CREB2. The CREB family of transcription regulators is highly conserved across evolution and represents the major switch involved in the transformation of short-term memory into long-term memory. The CREB target genes, whose transcription is regulated during consolidation, include a set of immediate-early genes (such as C/EBP or *zif*268) that affect transcription of downstream genes. This results in changes, both increase and decreases, in the expression of an array of proteins involved in protein synthesis, axon growth, synaptic structure and function (5, 11, 12). When synaptic strength has to be permanently potentiated, ribosomal proteins, neurotrophins, Ca^{2+}-binding proteins, proteins involved in the exo-endocytotic cycle of synaptic vesicles and neurotransmitter receptors become upregulated, whereas cell
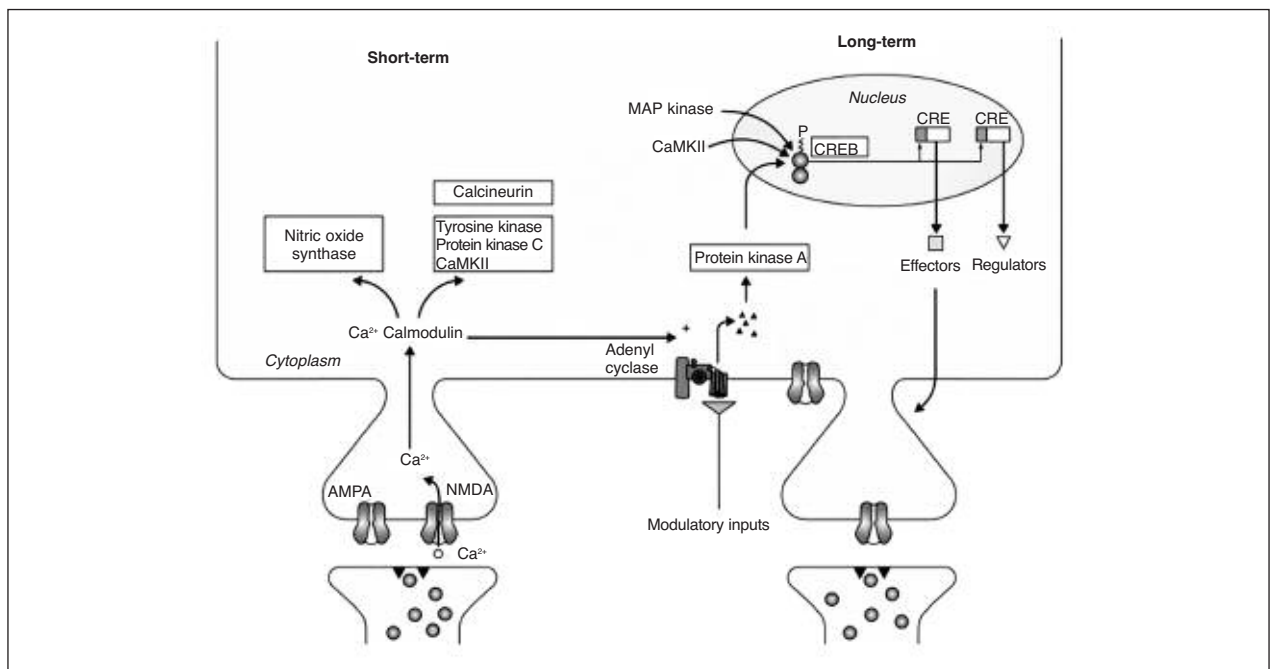

Figure 6. Molecular mechanisms of short- and long-term memory. In the figure the two identified coincidence detectors, namely adenylyl cyclase and NMDA glutamate receptors, are shown. Short-term memory processes consist of short-lived functional changes in synaptic strength, while long-term memory processes involve gene transcription and synthesis of new proteins responsible for structural changes.

adhesion molecules that usually maintain synaptic stability become downregulated. These specific changes in protein expression favour growth of terminal axon branches and establishments of novel synaptic contacts. Opposite phenomena are believed to occur in case of long-term depression of synaptic strength, favouring a decrease in the number of synaptic connections and/or a decreased activity of the existing synapses (Fig. 6).

Molecular mechanisms of implicit memory

As the simplest paradigms of implicit memory are elementary form of non-associative and associative behaviours present in primitive animals, they were very effectively studied in molluscs, particularly the sea snail *Aplysia californica*, that has a very simple central nervous system made by a few thousands neurons (about 15000-20000 in *Aplysia*) as compared to the high complexity of mammalian brain (about 10^{11}-10^{12} neurons in the human brain). *Aplysia* is able to learn very peculiar behaviours that, upon practice, can be consolidated into long-term memories. The animal learns to respond progressively more weakly to repeated innocuous stimuli (e.g. a light tactile stimulus), a behaviour called *habituation*, and to reinforce the response to repeated noxious stimuli (e.g. a painful electrical shock), a behaviour known as *sensitization*. In both cases, the synaptic efficiency in the integration centre of a sensory-motor reflex is changed by experience, leading to an increased response of the reflex in the case of sensitization or in a reflex inhibition in the case of habituation. Both changes are integrated at the presynaptic level, mediated by changes in the Ca^{2+} influx in response to the action potential. In habituation, Ca^{2+} influx is decreased into the sensory neuron terminal and the release of the neurotransmitter glutamate is accordingly decreased (synaptic depression). In sensitization, on the contrary, the activity of a facilitating serotonergic interneuron increases cyclic AMP concentration into the sensory neuron terminal, leading to PKA activation, phosphorylation of a potassium channel, lengthening of the depolarization evoked by the action potential and larger influx of Ca^{2+} increased glutamate release (synaptic potentiation). It is noteworthy that these two

opposite forms of learning are associated with opposite changes in synaptic strength at the same integration centre of a somatic reflex arc (1, 5).

Aplysia also exhibits a more complex form of associative learning, typical of higher animals, known as classical conditioning. In this learning paradigm, the beast is given a strong and painful unconditioned stimulus (that if administered alone would produce sensitization) in association with a weak, innocuous, conditioned stimulus (that if administered alone would produce habituation). Following the repeated pairing of these two stimuli over the trials, the animal learns to associate the two stimuli and to react to the isolated conditioned stimulus with an enhanced response (greater than sensitization to the noxious stimulus). The classical conditioning is reflected in the neural circuitry as a greatly enhanced synaptic strength of the input connections between the sensory neuron and the motor neuron. At variance with non-conditioned learning, this potentiation involves both presynaptic and postsynaptic mechanisms. The coincidence of the two stimuli is revealed by specific coincidence detectors located on both sides of the synapse. At the presynaptic level, the coincidence detector is adenylyl cyclase whose response to G protein-mediated activation is potentiated by Ca^{2+}/calmodulin binding following the increase in Ca^{2+} influx promoted by the activation of the conditioned pathway. On the postsynaptic side, the coincidence detector is the ligand- and voltage-operated glutamate NMDA receptor. This Ca^{2+} channel cannot be opened by glutamate alone because, when the postsynaptic neuron is in the resting state, the channel is blocked by Mg^{2+} ions. However, when glutamate release is associated with postsynaptic depolarization, as it happens when the conditioned stimulus is paired with the unconditioned one, the Mg^{2+} block is removed and the channel can open. Under these conditions, Ca^{2+} influx triggers signal transduction cascades leading to activation of protein kinases, phosphorylation of receptors and activation of multiple enzyme cascades (1,5). This simple model also tells us that in all forms of memories involving association among events, the key mechanisms is a coincidence detector, i.e. a signal transducer that requires the convergence of at least two distinct input stimuli (e.g. G protein activation plus Ca^{2+}/calmodulin stimulation

for adenylyl cyclase or glutamate release plus postsynaptic depolarization for NMDA glutamate receptors; see Fig. 6).

Molecular mechanisms of explicit memory

The studies on the mechanisms involved in explicit memory are more complex, as explicit memory involves a conscious recall and the integration of multiple sensory inputs. Thus, these studies are not feasible in invertebrates and lower vertebrates and require the complexity of the mammalian nervous system. Studies addressing the molecular mechanisms of such explicit memory in mammals profited by the possibility of manipulating the mouse genome by knocking out or overexpressing single proteins in the brain or in specific neuronal populations, studying synaptic plasticity at network level (e.g. in hippocampal slices) and evaluating explicit memory by behavioural tests for spatial memory and object recognition. In the mouse (and man), the brain area that plays a central role in this type of conscious learning is the hippocampus. Direct experimental evidence proves the involvement of hippocampus in all kinds of explicit memory, and particularly in spatial memory. The case of H.M., in which the patient lost after hippocampectomy the possibility of acquiring new conscious memories, as well as functional MRI studies, demonstrating an activation of the medial temporal lobe in all tasks in which the subject memorize a map or mentally rehearse an itinerary, indicate the importance of the hippocampus in various forms of conscious memory. Moreover, studies in rodent hippocampus have revealed the existence of *"place cells"*, whose firing is primarily controlled by the position of the individual and by distant visual cues, that create an internal representation of the animal's location with respect to the surrounding environment. Finally, the hippocampus exhibits the most known and extensively studied form of synaptic plasticity, namely long-term potentiation (LTP) (1, 5, 13).

A large amount of studies demonstrated that LTP is indeed a valid model of "memory storage": hippocampal LTP can be induced by animal experience and, conversely, conscious learning is impaired under conditions in which LTP is impaired or abolished. LTP has all the features required to be the cellular mechanism of explicit memory as it is associative in nature, is triggered by the coincidence of events and can be activated by endogenous patterns of electrical activity (e.g. the Q rhythm). The molecular mechanisms that mediate the generation of hippocampal LTP are surprisingly conserved across evolution and are closely similar to the mechanisms of associative learning identified in invertebrates. Thus, both pre- and postsynaptic mechanisms participate in the early phase of LTP expression, with a coincidence detector represented in most cases by NMDA glutamate receptors that trigger activation of multiple kinase pathways, including CaMKII, and generation of retrograde messengers. Moreover, the late phase of LTP involves CREB activation and regulation of transcription of the CREB target genes and is blocked by drugs inhibiting protein and/or mRNA synthesis (13-15).

Memory needs time to be stabilized in the hippocampus before the final storage. In fact, LTP induced by an experience is inhibited by a novel experience administered soon (within 1 hour) after the first one, whereas an LTP established for more than 1 hour is immune to this reversal mechanism. These observations suggest that the critical event in determining the retention of information may consist in the stabilization of the potentiated hippocampal synapses in order to resist to LTP reversal upon new information (14). Although hippocampus is fundamental to acquire new memories, it appears to be dispensable after the memory has been fully consolidated. In fact, although the patient H.M. was totally unable to build up new memories, he was still able to remember his past life preceding the bilateral ablation of the hippocampi. This indicates that permanent memories are distributed among different cortical regions according to the various perceptual features and that these various aspects are linked so that, upon recall, the different components of a memory are bound together to reproduce the memory in its integrity. This process appears to be time-dependent and hippocampus is still necessary to bind together the components of recent memories, whereas more remote explicit memories can be recalled independently of the hippocampus as the connections between cortical representation strengthen. It is

currently believed that this memory transfer process occurs largely during sleep, particularly the REM sleep (5, 11).

Conclusions

In conclusion, this article has briefly summarized the current views on the forms, theories and cellular mechanisms of learning and memory. Virtually all the experimental evidence, both direct and indirect, indicate that: (i) all forms of memory from the simplest to the most complex ones, are encoded as plastic changes in synaptic connections sharing a common molecular alphabet and (ii) notwithstanding the differences between implicit and explicit memory systems and the distinct brain areas involved, the cellular and molecular mechanisms are closely similar and appear to utilize elements of a common genetic program. The film master Luis Buñuel wrote that "*it is necessary to begin to loose memory, even only in part, to grasp that it is memory that fills up our lives. Life without memory is not life, as intelligence without the possibility to express it is not really intelligence. Memory is our coherence, our reason, our feeling, even our action. Without it, we are nothing.*"

From these words it is clear that memory is not just an ability to store information, but is the essence of our beings, the basis of our individuality and our consciousness. Each individual knows that he/she is unique, not merely because of his/her external appearance, but for his/her personal history, behaviour and ability to face daily life. As summarized above, the various forms of learning and memory, although they become more and more complex with evolution, share common cellular mechanisms of neural plasticity. These physiological mechanisms have been partially elucidated at synapse and network levels, but we are only beginning to understand its complexity at systems level. The Nobel laureate Francois Jacob wrote: "*The past century was focused on nucleic acids and proteins*" The next century will focus on the mechanisms of memory and desire. Will we be able to answer to the questions that will be addressed?*". Although many questions remain about the relationship between the intracellular biochemical processes, the plasticity of neuronal networks and memory, we all hope that Neuro-

science research will be able to win this challenge in the near future.

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