How Does Electroconvulsive Therapy Work? Theories on Its Mechanism

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This article reviews 3 current theories of electroconvulsive therapy (ECT). One theory points to generalized seizures as essential for the therapeutic efficacy of ECT. Another theory highlights the normalization of neuroendocrine dysfunction in melancholic depression as a result of ECT. A third theory is based on recent findings of increased hippocampal neurogenesis and synaptogenesis in experimental animals given electroconvulsive seizures. Presently, the endocrine theory has the strongest foundation to explain the working mechanism of ECT.

Can J Psychiatry. 2011;56(1):13–18.

Clinical Implications

- Appropriate application of ECT implies that generalization of seizures is ascertained. Subconvulsive seizures should be avoided, as they produce cognitive impairment and no therapeutic effect.
- Severely depressed patients should be carefully examined for symptoms and signs of melancholia, in particular vegetative phenomena, as such patients respond better to ECT than to pharmacotherapy—and not to psychotherapy or social interventions.

Limitations

- Theories of the mechanism of ECT can only partly explain the efficacy of ECT in depression. It is an unresolved issue as to whether ECT efficacy in other conditions (mania, catatonia, delirium, and psychosis) is due to common features of these clinically varied conditions or to a single mechanism of action.
- The finding that generalized seizures induce a sustained formation of new neurons in the hippocampus and an increase in the number of newly formed synapses has, so far, been shown only in animal studies. The relevance of these neurotrophic effects for ECT effects on neuroendocrine functions await further research in humans.

Key Words: *electroconvulsive therapy, theory, seizures, mechanism, neurogenesis, hypothalamus, hippocampus, melancholic depression*

Since the introduction of ECT in 1938, the mechanism of action of this highly effective treatment[1–4] has intrigued psychiatrists and neuroscientists. The inventor of convulsive therapy, Ladislas Meduna,[5] suggested that chemically induced seizures were effective in the treatment of schizophrenia by "changing the chemical composition of the brain."[6, p 51] In the course of ECT, an electrical current traverses brain tissue and a grand mal seizure is evoked; it is inevitable that events such as these will have major physiological consequences.

During the 75 years of ECT history, a wealth of theories regarding its mechanism of action have been suggested. Some are based on important aspects of the convulsive therapy process, while others, such as several psychological theories, rest on speculations inspired by the prevailing psychodynamic theories for psychiatric illness and treatment of their day.

A 1979 overview of theories separated the theories into structural, psychological, electrophysiologic, and biochemical theories.[7]

The structural theories that pointed to the hypothalamus[8,9] should be mentioned in particular, as they suggested that the electrical stimulation has a physical effect on the pituitary or the frontal regions of the brain, pointing to modern lines of thinking. Later studies[10,11] suggested an important role of brain stem centres, particularly the hypothalamus.

Among psychological theories, the idea of ECT inducing punishment found support from the greater efficacy in patients with melancholic depression, those dominated by guilt and preoccupation with suicide. This idea, like the thoughts of ECT eliciting primitive adaptations to various forms of denial of illness or anosognosia, have long ago been abandoned.

Other psychological theories built on treatment-induced amnesia as the therapeutic agent attracted some interest and led to many studies.[7]

With the development of unilateral ECT that made it possible to separate the AD from the amnesic effects of ECT,[12] the amnesia theories no longer have any scientific merit.

Electrophysiological theories were based on the science of electroencephalography and a wealth of studies documented the role of both seizure and interseizure recordings relating to ECT (for a review, see Fink[7]).

Among biochemical–neurochemical theories, attention has been focused on neuropeptides and a brain stem locus of activity.[7]

Biochemical hypotheses are under steady development, moving from a focus on monoamines to neuroreceptors to neurotropic factors and lately to gene products. Despite coherent neurochemical hypotheses regarding mood disorders (serotonin hypothesis) and schizophrenia (dopamine hypothesis), other neurotransmitter systems are now of interest; for example, glutamate or gamma-aminobutyric acid, none of which meet all aspects of the complex neurochemistry of psychiatric disorders. ECT seems to alter virtually every neurotransmitter system; therefore, at present, it is impossible to discern the essential effects.[13]

Abbreviations used in this article

AD	antidepressant
AVP	arginine vasopressin
BDNF	brain-derived neurotrophic factor
DST	Dexamethasone Supression Test
ECS	electroconvulsive shock
ECT	electroconvulsive therapy
EEG	electroencephalogram
HPA	hypothalamic–pituitary–adrenal
MRI	magnetic resonance imaging
NPY	neuropeptide Y
PVN	paraventricular nucleus
SON	supraoptic nucleus
TMS	transcranial magnetic stimulation
VMH	ventromedial nucleus
VNS	vagus nerve stimulation

Any formulation of the mechanism of ECT will encounter numerous difficulties. ECT is effective in various illnesses such as depression, mania, schizophrenia, and catatonia, but it remains an unresolved issue whether ECT exerts differential effects, or whether these obviously different disorders have common pathophysiological bases.

A useful theory of ECT should therefore not be restricted to the AD effect; however, as the etiology and pathophysiology of mood disorders and schizophrenia are far from unravelled, a theory of ECT mechanism cannot be complete.

Among hypotheses of the working action of ECT,[13] 3 hypotheses are prominent today:

1. The generalized seizure theory
2. The neuroendocrine–diencephalic theory
3. A combined anatomical–ictal theory (generalized seizures with an effect on critical brain regions)

The Generalized Seizure Theory

This theory enounces that the therapeutic effect of ECT is dependent on the elicitation of generalized seizures.

In Sweden, Ottosson[12] was the first to demonstrate that generalized seizures are essential for the therapeutic effect of ECT, and that subconvulsive stimuli had weaker or no AD effect. Seizure generalization can be estimated from ictal EEG amplitude, coherence and postictal suppression criteria, and from such physiological measures as heart rate and prolactin response.[14,15]

The greater the generalization of a seizure the stronger the brain stem is activated. Recent single photon emission computed tomography studies looking at several brain regions during ECT suggest the relevance of an extended activation of cortico–thalamic–cortical circuits for the efficacy of seizure therapy.[16]

Promoting a seizure in cortical regions that funnel into centrencephalic structures is consistent with the generalization theory.

Evidence for the Theory

1. Studies of real, compared with sham, ECT show that the latter have no effect.
2. Bilateral electrode placement, which induces more pronounced seizure generalization than unilateral electrode placement, has superior therapeutic efficacy.
3. ECT and flurothyl inhalation induce similar seizure activity and equivalent clinical effects.
4. Nonconvulsive methods of brain stimulation (TMS and VNS) have weak therapeutic effects, not clearly distinguishable from sham treatments.[17–19]

Limitations of the Theory

Despite a large number of preclinical studies finding seizures to exert neurotrophic effects, such as neurogenesis, neuronal sprouting, and neurogenesis,[13] their clinical relevance remains unclear. They may point to ECT having nurturing and regenerating effects, but these changes have not yet been demonstrated in humans.

In summary, generalized and repeated seizures affecting centrencephalic structures—and most likely also prefrontal regions—represent a necessary, yet not always sufficient, condition for ECT efficacy. The generalization theory, however strong, cannot stand alone.

The Neuroendocrine–Diencephalic Theory

This theory enounces that ECT works by restoring neuroendocrine dysfunction associated with melancholic depression.

Severe depression (melancholia) is accompanied by a dysfunction of the HPA axis.[20,21] There is a disturbed hormonal secretion, particularly of cortisol. Cortisol and several other hormones have psychotropic effects, and their excesses or deficiencies induce states of mania or depression.[20]

After finding superiority of bilateral over unilateral ECT, Abrams and Taylor,[11] in 1976, suggested that diencephalic stimulation is a prerequisite for the therapeutic benefit of ECT in endogenous (melancholic) depression.

It was the relief exerted by ECT of melancholic features of disturbed sleep, appetite, and sexual drive during depression or mania, pointing to a strong involvement of the hypothalamus, that led Fink and Ottosson[22] to propose their neuroendocrine theory of the working action of ECT:

> The AD efficacy of convulsive therapy results from the persistent release of hypothalamic substances that mediate mood changes from depression to normal mood states with attendant modifications in vegetative functions.[p 50]

Evidence for the Theory

Favouring the endocrine theory of ECT mechanism is the evidence that ECT induces wide release of endocrines, numerous endocrine responses in humans, such as elevated plasma concentrations of prolactin,[23] adrenocorticotropin,[24] AVP,[25–28] and NPY.[29] All are hormones related to the HPA axis, which appears dysregulated during severe depression.[20] Other neuropeptide hormones, not associated with the HPA axis, fail to show hypersecretion during ECT.[28]

NPY, which, together with its receptors, is thought to have a direct implication in depression,[29] is decreased in cerebrospinal fluid of depressed patients[30] and increased after ECT.[31,32]

Also, most patients with untreated melancolia and elevated plasma cortisol with an abnormal DST show normalized DST after successful ECT,[33,34] emphazising the role of the hypothalamus.

Finally, selectively increased blood flow measured with positron emission tomography in the basal ganglia, brain stem, and diencephalon following ECT demonstrates that centrencephalic structures are stimulated by the treatment.[35]

Findings to support a measurable neuroendocrine involvement with nonconvulsive methods (repetitive TMS and VNS) comparable to that of ECT are lacking, probably because these treatment modalities do not engage centrencephalic centres.

Limitations of the Theory

Symptoms thought to arise from disturbed hypothalamic function, such as disturbed sleep, appetite, and libido, can occur outside mood episodes, and are therefore not specific to melancholia.

Also, owing to the close interconnection between the limbic system and the hypothalamus, generalized seizures inevitably involve stimulation of the hypothalamus, with massive activation of the sympathetic nervous system, including increased heart rate, blood pressure, and hormone levels,[24] and may thus be sequelae of the seizure activity, rather than the therapeutic agent.[13,36]

The putative role of the hippocampus is discussed in connection with the phenomenon of neurogenesis (discussed below).

In summary, despite the limitations mentioned, the wealth of clinical supportive data justifies the decade-long prominent role of this theory.

Suggested Anatomical Models

While the 2 aforementioned hypotheses imply an indirect influence on cortical structures (the prefrontal lobe), another model[13] suggests that the crucial mechanism behind AD effect is to be found in the direct stimulation of the prefrontal cortex, a region considered critical for the integration of cognition and emotion.

The greater efficacy of bilateral electrode placement (bifrontal and bitemporal) stimulation than of unilateral—except with very high doses[37]—is in accordance with this notion, as is the association between clinical improvement and greater prefrontal slowing of the EEG activity.[38]

The image of a robust stimulation of the brain region most likely to represent the neural underpinning of intellectual activity related to emotion and the self is immediately obvious, with the prefrontal area preferred by several researchers.[39,40]

However, for a hypothesis or theory that may explain the effect of brain stimulation also on the somatic–vegetative disturbances

—the hallmark of melancholic depression—an anatomical model should include the limbic system and the brain stem.

A Combined Anatomical–Ictal Theory

This theory enounces that seizure activity in the limbic system induces neurotrophic effects crucial for the therapeutic efficacy of ECT.

Evidence for the Theory

Human Data. MRI studies in depressed patients finds the volumes of both the right and the left hippocampi to decrease, with a correlation between the duration of untreated depression and the MRI findings.[41,42]

MRI studies conducted before and 1 week after a series of ECT find increases in both right and left hippocampal volume after ECT.[43]

Animal Data. Neurogenesis increases after ECSs. The first report in 2000 by Madsen et al[44] (see also Bolwig and Madsen[45]) of a strong increase in rat hippocampal neurogenesis after ECS showed that both a single seizure and a series of seizures induced neurogenesis in the dentate gyrus of the hippocampus in a dose-response related manner. Importantly, this effect was sustained and still observable for at least 3 months.

These findings were quickly replicated by several independent research groups, mainly in rodents. Interestingly, a study by Perera et al[46] demonstrated identical findings in adult nonhuman primates; their findings further support the possibility that ECT may produce similar alterations in the human brain.

Neurogenesis is vulnerable to various stressors, represented in animal models of depression, and also to increased blood levels of cortisol. Hypercortisolemia is therefore relevant for the theory as it is also found in patients with melancholia, many of whom are nonsuppressors when administered the DST.[47]

The newborn cells are functional and form new synapses. Chen et al[48] found a highly significant increase in the number of synapses and an increased synaptic density in the CA1 area of the hippocampus in unchallenged rats given ECS. Cellular functionality was thus demonstrated, sustaining earlier[49,50] suggestions of hippocampal synaptogenesis resulting from ECS.

High levels of cortisol suppress hippocampal neurogenesis.[51] To test whether this suppressive effect of cortisol on hippocampal neurogenesis could be reversed by ECS, Hellsten et al[52] treated rats with high doses of corticosterone, which completely abolished neurogenesis in the dentate gyrus. Repeated ECS reversed neurogenesis to normal levels. This animal study is in good accordance with clinical findings.

BDNF, a protein that assures survival and growth of new neurons and synapses, is widespread in the brain and peripheral nervous system. Increases in this important protein following ECS are more pronounced in limbic structures (hippocampus and enthorinal cortex) than in other regions. Similar to the early studies of brain-specific proteins and ECS,[49,50] the increases of BDNF are dose-dependent and sustained.[52]

Of further interest is the finding by Malberg et al[53] that suppression of hippocampal neurogenesis is diminished both by ADs (tranylcypromine, reboxetine) and by ECS. However, the effect of ECS is significantly stronger than that of drugs.

High-throughput technologies that enable parallel studies of genomic changes involving thousands of genes have been developed, but are, so far, applicable only in animal studies. An example from such relevant animal studies is the finding that ECSs alter gene transcription in different brain regions. After both acute and chronic ECSs there were changes in 120 unique genes, especially in the hippocampus, less so in the frontal cortex.[54] At the genomic level, these studies further demonstrate that the chronic effects of ECT are mediated in the hippocampus rather than in the frontal cortex.

As in the clinical situation, upregulation of neurogenesis is dependent on chronic exposure to ECS, consistent with the time course for the therapeutic action of clinically administered ECT.

Limitations of the Theory

Human Data. The human data are based on relatively few patient groups, and further validation of the conditions studied is warranted.

Animal Data. The animal data are based on unchallenged animals or they apply experimental models useful only in studies of stress and anxiety; none of these models can be considered valid for major (melancholic) depression or schizophrenia in humans.

The data supporting the idea of an important influence on the efficacy of ECT of neurotrophic effects, including neurogenesis, are in line with the notion that severe depressive illness can arise from impaired neurogenesis and that an array of ADs are active by stimulating such neurogenesis (the neurogenesis hypothesis).[21]

Recent Experimental Data Lend Support to the Neuroendocrine–Diencephalic Theory

Applying the same principles as those used in several of the studies that have focused on the hippocampus (bromodeoxy-uridine to detect cell proliferation, and c-fos immunohistochemistry), it has recently been possible to identify relevant cell assemblies in rat hypothalamus and their reaction to ECS.

Thus Jansson et al,[55] in a series of elegant studies, demonstrated a correlated pattern of increases in neuronal activation and increased endothelial cell proliferation in the PVN, the SON, and the VMH of the hypothalamus after ECS in rats.

PVN and the neurons of the SON produce the neuropeptide oxytocin, which has anxiolytic properties,[56] and AVP, which acts in synergy with the corticotropin-releasing hormone.

VMH is involved in the regulation of appetite, and neurons in this region secrete NPY; VMH is further thought to participate in circadian regulation of sleep and waking.[57]

The nuclei within the mid-hypothalamus are heavily interconnected and share many regulatory functions.

If these experimental findings can be replicated in humans it may be speculated that the disturbed hypothalamic functions in patients suffering from mood disorders are caused by a dysfunctional interplay between hypothalamic centres. So far it can be concluded that mid-hypothalamic regions displaying neuronal activation and endothelial cell proliferation in response to ECS treatment may well be involved in the pathophysiology of affective disorders.[51]

While the neuroendocrine theory[19] is unchallenged, the role of hippocampal influence on the working action of ECT should not be dismissed.

It is unlikely that the hippocampus and not the hypothalamus—or vice versa—is activated by generalized seizures.

Therefore, an elucidation of the interconnection between these regions, not least regarding the time course of seizure-induced biochemical events, should be considered highly important for the formulation of a coherent neurobiological theory of the working action of ECT.

Conclusions

The efficacy of ECT in the therapy of severe depression—and most likely also in other conditions—is dependent on the elicitation of generalized seizures.

However, the generalized seizure theory explains neither the neurochemical consequences of seizures nor the beneficial and unwelcome behavioural effects of treatments.

Generalized seizures exert a strong influence on diencephalic structures, and the neuroendocrine–diencephalic theory rests on findings supporting a key role of the hypothalamus for amelioration of symptoms of melancholic depression. Generalized seizures induce neurotrophic changes such as neurogenesis and synaptogenesis in hippocampus.

A strengthening of the neurogenesis theory with patient data may elucidate fundamental mechanisms of action of ECT at the cellular and molecular level, and replicating the preclinical findings in humans should therefore have high priority.

Presently, the neuroendocrine–diencephalic theory has the strongest foundation among existing theories to explain the working mechanism of ECT.

Acknowledgements

The Canadian Psychiatric Association proudly supports the In Review series by providing an honorarium to the authors.

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Manuscript received, revised, and accepted June 2010.

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Résumé : Comment fonctionne l'électroconvulsothérapie? Des théories sur son mécanisme

Cet article examine 3 théories actuelles de l'électroconvulsothérapie (ECT). Une théorie indique que les convulsions généralisées sont essentielles à l'efficacité thérapeutique de l'ECT. Une autre théorie souligne la normalisation de la dysfonction neuroendocrine dans la dépression mélancolique par suite de l'ECT. Une troisième théorie se base sur des résultats récents de neurogenèse et de synaptogénèse hippocampiques accrues chez des animaux de laboratoire à qui l'on a administré des convulsions d'ECT. Présentement, la théorie endocrine a le fondement le plus solide pour expliquer le mécanisme de fonctionnement de l'ECT.