# THE MECHANISM OF ACTION OF ECT



- Theoretical contributions
- Original research

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### A Primer for the Conceptualization of the Mechanism of Action of Electroconvulsive Therapy, 1: Defining the Question

Chittaranjan Andrade, MD



Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

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#### ABSTRACT

With regard to the question of how electroconvulsive therapy (ECT) acts, a common answer is that the mechanism of action of the treatment is not well understood. However, this

#### **Clinical Problem**

Mr D, a 35-year-old man with major depressive disorder, has been severely depressed for the past 6 months. He has failed 2 adequate antidepressant trials, one of which was with a dual-acting antidepressant drug. He has also failed 1 trial of antidepressant augmentation with an atypical antipsychotic drug. Presently, he has severe social and occupational impairment as well as active suicidal ideation. Electroconvulsive therapy (ECT) has been suggested to him. Mr D is doubtful; he wants to know why electricity needs to be passed into his brain and how ECT acts. How should the clinician respond?

ECT is arguably the most effective treatment available for major mental illness. ECT is commonly advised when the patient is catatonic, suicidal, very severely ill, or unresponsive to medications.<sup>1</sup> When ECT is discussed, a common question addresses the mechanism of action of the treatment: How does ECT work?

This question is asked by patients, relatives of patients, members

Practical Psychopharmacology

### A Primer for the Conceptualization of the Mechanism of Action of Electroconvulsive Therapy, 2: Organizing the Information

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#### ABSTRACT

Much literature is available on the effects of electroconvulsive therapy (ECT) in the brain. Clinicians need to know how to organize this information when they explain hypotheses about the mechanism of action of ECT to patients and caregivers. One possibility is to classify the data under the headings of delivery

#### **Clinical Problem**

The previous article in this column<sup>1</sup> presented an antidepressantrefractory, severely depressed patient for whom electroconvulsive therapy (ECT) had been suggested. The patient had asked why it was necessary for electricity to be passed through his brain. He wanted to know how ECT acts. The article<sup>1</sup> explained why the question about the mechanism of action of ECT is a complex one and why it needs to be resolved into specific elements. The article also explained difficulties in the interpretation of research and academic concerns related to the generation of explanatory models. The present article deals with the problem of plenty; that is, how the large body of evidence on the subject may be organized so as to generate coherent explanations about the mechanism of action of ECT.

Much evidence is available on the electrophysiologic, neurochemical, neurotransmitter, neuroendocrine, histologic, and other changes that result with ECT, most or all of which have been offered as explanations for its mechanism of action. A considerable problem that one faces is to understand which of these changes are therapeutic and which are epiphenomena; which of the therapeutic changes are upstream and which

## Electroconvulsive Therapy, Hypertensive Surge, Blood-Brain Barrier Breach, and Amnesia Exploring the Evidence for a Connection

Chittaranjan Andrade, MD\* and Tom G. Bolwig, MD, DMSc†

Abstract: Preclinical and clinical evidence show that electroconvulsive therapy (ECT)-induced intraictal surge in blood pressure may result in a small, transient breach in the blood-brain barrier, leading to mild cerebral edema and a possible leach of noxious substances from blood into brain tissues. These changes may impair neuronal functioning and contribute to the mechanisms underlying ECT-induced cognitive deficits. Some but not all clinical data on the subject suggest that blood pressure changes during ECT correlate with indices of cognitive impairment. In animal models, pharmacological manipulations of blood pressure during electroconvulsive shocks attenuate electroconvulsive shock-induced amnestic changes; however, the evidence suggests that antihypertensive mechanisms may not necessarily be involved. Clinical studies involving BP sharply increases by 30% to 40%, with systolic pressure rising more than diastolic pressure. The increase is greater in men than in women and in hypertensive patients than in normotensive patients. In some patients, especially those who receive anticholinergic medications, the systolic hypertensive surge may even exceed 200 mm Hg. There is a sharp drop in BP immediately after the seizure, and baseline or near-baseline levels are attained within a few minutes of the end of the seizure.<sup>1,6</sup>

### ECT AND BBB BREACH

The earliest studies of the BBB during pentylenetetrazol (PTZ)- or ECT-induced convulsions were conducted in animal

## HOW DOES ECT WORK?

- Common, defensive answer: The mechanism of action of ECT is unknown, but a seizure is necessary for it to be therapeutic.
- Comment: Would we say, "The mechanism of action of paroxetine is unknown, but serotonin reuptake inhibition is necessary for it to be therapeutic?"
- People are used to receiving drugs, not electricity, as treatment.



- What is the mechanism of action of paroxetine?
- SSRI, anticholinergic
- Are synaptic explanations sufficient?
- Is depression so simply understood?
- What the drug does vs mechanism of action
- There is a library of information about what ECT does
- There are speculations about how ECT acts

PURPOSE OF THIS PRESENTATION

- To discuss ONLY histological explanations for the mechanism of action of ECT in depression and ECT-related amnesia.
- This may represent a final common pathway.
  - There may be more than one final common pathway.
- This can be communicated to professional colleagues, patients, and caregivers.

# LOBES OF THE BRAIN



- Prefrontal cortex (PFC)
- Dorsolateral
  PFC
- Ventromedial PFC
- Orbitofrontal PFC



### CROSS SECTION

Corpus collosion A large band of nerve fibers through which information flows back and forth between the left and the right hemispheres of the brain

Thalamus-

The relay station for most information going into the brain

Hypotisalanes Regulates sex bormones, blood pressure and body temperature

Pituitary gland The master stand

The master gland of the body produces its own hormones and also influences the hormonal production of the other glands in the body

Anygdala Regulates the leartbest and other visceral functions and processes the emotion fear

Hippocampus Helps establish long-term memory in regions of the corebral cortex

Poins

Spinal cord

Medulla

obionisata

Correbellium Essential for coordination of movement

> Control of broathing, circulation, heartbeat and digestion

THE Open's by Same Nam. These Manufact Rap. Fact A radd

Basal ganglia A control system for movement and coasitive functions

## AMYGDALA AND HIPPOCAMPUS



# SOME BASIC CONCEPTS

- Hippocampus = dentate gyrus + Ammon's horn (CA4, CA3, CA2, CA1) + subiculum + presubiculum and parasubiculum.
- Neurogenesis occurs in the subgranule layer of the dentate gyrus; the new cells migrate into the granule layer.
- Granule cells of the DG send their axons (called "mossy fibers") to CA3.

STRESS AND DEPRESSION (Andrade and Rao, Indian J Psychiatry 2010)

- Stress and depression are associated with decreased neuroplasticity in the hippocampus and PFC, and increased neuroplasticity in the amygdala.
  - Preclinical and clinical evidence
  - Gross and microscopic evidence
- Antidepressants reverse most of these changes.
  - Neurogenesis
  - Dendritic arborization, new synapse formation
  - Gliogenesis
  - Implications

- ECS induces nerve cell proliferation in the hippocampus.
- The number of new neurons formed increases with an increase in the number of ECT.
- The new neurons differentiate and survive for at least 3 months.
- (Scott et al, Exp Neurol 2000; Madsen et al, Biol Psychiatry 2000; Hellsten et al, Eur J Neurosci 2002)

- Whereas glucocorticoids inhibit neurogenesis, ECSinduced hippocampal neurogenesis occurs even after chronic treatment with cortisol.
- This implies that ECT would stimulate hippocampal neurogenesis even in the presence of stressinduced hypercortisolemia.
- (Hellsten et al, Eur J Neurosci 2002)

- Whereas glucocorticoids also inhibit gliogenesis, ECS-induced hippocampal gliogenesis occurs even after chronic treatment with cortisol.
- This implies that ECT would stimulate hippocampal gliogenesis even in the presence of stress-induced hypercortisolemia.
- (Wennstrom et al, Biol Psychiatry 2002)

- ECS also stimulates vascular endothelial proliferation in the hippocampus.
- This probably supports the new neurons and glia that are formed after ECS.
- (Hellsten et al, Biol Psychiatry 2004; Newton et al, Eur J Neurosci 2006)
- This endothelial response is due to the ECS itself, and not to the hypoxia associated with unmodified ECS (Hellsten et al, 2005).

# ECT AND NEUROPLASTICITY Amygdala

- Repeated ECS induces glial cell proliferation in the amygdala.
- The proliferation remains evident 3 weeks later, when some of the new cells show differentiation into mature oligodendrocytes
- (Wennstrom et al, Biol Psychiatry 2004)

## ECT AND NEUROPLASTICITY Prefrontal cortex and hypothalamus

- Repeated ECS stimulates vascular and glial (but not neuronal) proliferation in the frontal cortex (Madsen et al, Neuropsychopharmacol 2005).
- Repeated ECS-induced increase in neuronal activation and associated endothelial proliferation has also been recorded in the paraventricular nucleus, the supraoptic nucleus, and the ventromedial nucleus of the hypothalamus (Jansson et al, Biol Psychiatry 2006).

AFTER 10 ONCE-DAILY ECT: 1 (Chen et al, Eur Neuropsychopharmacol 2009)

- ECT increased the volume of the granule cell layer and hilus of the dentate gyrus.
- [No change in the volume of the pyramidal cell layer in CA1 and CA2/CA3, or of the stratum radiatum in CA1.]
- ECT increased the number of neurons in the granule cell layer.
- [No change in the number of neurons in CA1 and CA2/CA3.]

AFTER 10 ONCE-DAILY ECT: 2 (Chen et al, Eur Neuropsychopharmacol 2009)

- ECT increased the total number of synapses in CA1.
- ECT increased the number and percentage of spine synapses in CA1.
- [No change in the number of shaft synapses; decrease in the percentage of shaft synapses, indicating synaptic remodelling.]
- Note: Excitatory synapses are mostly formed on dendritic spines; and spine synapses are architecturally more efficient than shaft synapses.

AFTER 10 ONCE-DAILY ECT: 3 (Chen et al, Eur Neuropsychopharmacol 2009)

- Both perforated and nonperforated spine synapses were increased in CA1.
- Note: Perforated synapses show greater synaptic efficiency; and they may split into two or more nonperforated synapses.
- ECT increased synaptic height in CA1.
- Note: Increased synaptic height may improve the efficiency of synaptic remodelling.

### Images in Electroconvulsive Therapy

*Electroconvulsive Shocks Dose-Dependently Increase Dendritic Arborization in the CA1 Region of the Rat Hippocampus* 

Jangama S. M. Smitha, MSc (Medical Anatomy), \* Ravindranath Roopa, MBBS, MS (Anatomy), \* Nagarchi Khaleel, MSc (Medical Anatomy), \* Bindu M. Kutty, PhD, † and Chittaranjan Andrade, MD, ‡

Abstract: Stress and depression are associated with impaired neuroplasticity in the hippocampus: there is decreased dendritic arborization and synaptogenesis, which is hypothesized to explain decreased adaptive competence of the organism. Representative light microscopy images are presented that show that 6 once-daily electroconvulsive shocks (ECSs) dose-dependently increased dendritic arborization in the CA1 region of the hippocampus in healthy, adult, male Wistar rats (n = 10 in each of sham, 10-mC, and 40-mC ECS groups). These neuroplasticity changes, identified 1 month after the last ECS, may explain a part of the mechanism of action of electroconvulsive therapy in conditions such as depression.

Key Words: Electroconvulsive therapy, Electroconvulsive shocks, Hippocampus, Neuroplasticity, Depression

(JECT 2014;00: 00-00)

here is decreased dendritic arborization and synaptogenesis in the hippocampus in stressed animals and in animal models of of electroconvulsive shocks (ECSs) on the hippocampus? The images show representative coronal sections of the CA1 region of the hippocampus, taken at the same level, in nonstressed adult male Wistar rats (180–250 g) that received 6 once-daily ECSs in each of 3 conditions: sham ECS (n = 10), low-dose ECS (10 mC) (n = 10), or high-dose ECS (40 mC) (n = 10). All rats receiving true ECS experienced generalized convulsions of adequate duration. No rats were lost to spinal fracture or other reasons. The rats were housed under standard laboratory conditions for 1 month after the last sham or true ECS and were subsequently sacrificed for study of persistent hippocampal changes.

The mean length of the apical dendritic tree was significantly greater in rats receiving 40 mC ECS (Fig. 1) than in those receiving 10 mC ECS (Fig. 2) and significantly greater in rats receiving 10 mC ECS than in those receiving sham ECS (Fig. 3). The implication is that electroconvulsive therapy may dose-dependently restore the hippocampal neuroplasticity that is lost in depression,<sup>1,2</sup> thereby explaining at least a part of the mechanism of

### Images in Electroconvulsive Therapy ECS Dose-Dependently Increases Cell Proliferation in the Subgranular Region of the Rat Hippocampus

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**Abstract:** Stress and depression are associated with impaired neuroplasticity in the hippocampus; there is a decrease in neurogenesis, which is hypothesized to decrease the adaptative competence of the organism. Representative light microscopy images are presented which show that 6 once-daily electroconvulsive shocks (ECS) once daily, dose-dependently increased new cell formation in the subgranular region of the hippocampus in healthy adult male Wistar rats (10 sections per rat, 3 rats in each of sham ECS, 10 mC, and 40 mC groups). These neuroplasticity changes, demonstrated 1 month after the last ECS, may explain a part of the mechanism of action of electroconvulsive therapy in conditions such as depression.

Key Words: electroconvulsive therapy, electroconvulsive shocks, hippocampus, neuroplasticity, neurogenesis, depression

(JECT 2014;00: 00-00)

show representative coronal sections of the subgranular region of the hippocampus taken at the same level in nonstressed adult male Wistar rats (180–250 g) which received 6 ECSs once daily in each of 3 conditions: sham ECS (n = 3), low-dose (10 mC) ECS (n = 3), or high-dose (40 mC) ECS (n = 3). All rats receiving true ECS experienced generalized convulsions of adequate duration. No rats were lost to spinal fracture or other reasons. The rats were housed under standard laboratory conditions for 30 days after the last sham or true ECS and were subsequently sacrificed for the study of new cell formation.

Ten BrdU-stained sections were examined per rat, and the number of new cells identified in these sections was averaged for each rat. The mean number of new cells was significantly greater in rats receiving 40 mC ECS (Fig. 1A) than in those receiving 10 mC ECS (Fig. 1B) and significantly greater in rats receiv-

### Electroconvulsive Therapy Attenuates Dendritic Arborization in the Basolateral Amygdala

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Abstract: Stress and depression are associated with aberrant neuroplasticity in the amygdala: there is increased dendritic arborization and synaptogenesis, perhaps explaining the increased anxiety and fear that are often apparent in depressed patients. Light microscopy images are presented, which show that 6 once-daily high (but not low)-dose electroconvulsive shocks attenuated dendritic arborization in the basolateral amygdala of Wistar rats, which changes were apparent even 1 month after the last electroconvulsive shock. These changes may explain a part of the mechanism of action of electroconvulsive therapy in conditions such as depression and posttraumatic stress disorder. There is increased dendritic arborization and synaptogenesis in the amygdala in stressed animals and in animal models of depression. It is suggested that these changes represent fear learning and explain the anxiety, fear, and related dysfunctional moods experienced by depressed patients.<sup>1</sup> What is the effect of electroconvulsive therapy (ECT) on these changes? Figure 1 displays representative coronal sections of the basolateral amygdala, taken at the same level, in nonstressed male Wistar rats (180–250 g) receiving 6 once-daily electroconvulsive shocks (ECS) in each of 3 conditions: sham ECS, low-dose (10 mC) ECS, or high-dose (60 mC) ECS. The rats were housed under

# Images in electroconvulsive therapy: Pilot impressions suggesting that ECT reduces excitatory synapses in the basolateral amygdala

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#### ABSTRACT

**Background:** In animal models, stress and depression are associated with excitatory changes in the amygdala; this aberrant neuroplasticity may represent increased fear learning, explaining the anxiety, fear, and related symptoms that characterize clinical depression.

Materials and Methods: In a pilot investigation, we treated adult, male, Wistar rats with sham electroconvulsive shocks (ECS; n=3), low-dose ECS (10 mC; n=3), and high-dose ECS (60 mC; n=3). The rats were sacrificed 1 month after the last of 6 once-daily ECS and, after dissection, sections of the basolateral amygdala were examined using transmission electron microscopy under low (×11,000) and high (×30,000) magnification.

**Results:** In each group, 4 fields were examined under low magnification and 6 fields under high magnification. The number of excitatory synapses and the ratio of excitatory to inhibitory synapses were both numerically lower with ECS than with sham ECS, and the effect was stronger in the high-dose ECS group (statistical analyses were not performed because this was a pilot study).

Conclusions: By reducing the number of excitatory synapses and the ratio of excitatory to inhibitory synapses,

# ECT, Hippocampus, and Amygdala

- Adult, male, Wistar rats
- 6 once-daily sham, 10 mC, or 40/60 mC ECS
- Animals sacrificed 1 month after the last ECS
- Hippocampus studied:
  - Pyramidal neurons in CA1: Light microscopy at 10x
  - BrdU staining in subgranular zone of DG: Light microscopy at 40x
- Basolateral amygdala studied
  - Apical dendrite and nodes: Light microscopy at 40x
  - Synapses: Electron microscopy @ 11,000x and 30,000x



- Pyramidal neurons showing dendritic arborization.
- 6 once-daily sham
  ECS
- 10x magnification



- Pyramidal neurons showing dendritic arborization.
- 6 once-daily 10 mC
  ECT
- 10x magnification



- Pyramidal neurons showing dendritic arborization.
- 6 once-daily 40 mC ECS
- 10x magnification



 BrdU stained new cells formed in the subgranular zone of the dentate gyrus.

- 6 once-daily sham
  ECS
- 40x magnification



- BrdU stained new cells formed in the subgranular zone of the dentate gyrus.
- 6 once-daily 10 mC ECS
- 40x magnification



- BrdU stained new cells formed in the subgranular zone of the dentate gyrus.
- 6 once-daily 40 mC ECS
- 40x magnification

HIPPOCAMPAL CHANGES AFTER 6 ONCE-DAILY SHAM, 10 mC or 40 mC ECS

## ECS is associated with dose-dependent:

- Increase in dendritic arborization
- Increase in new cell formation
- [Differentiation of these new cells not studied]
- Implications
  - Favors adaptative learning, coping?
  - Impairs memory by disturbing existing networks?
  - Mossy fibre sprouting may have the same effect
  - (Lamont et al, Br Res 2001; Akers et al, Science 2014)

## AMYGDALA CHANGES AFTER 6 ECS: Sham, 10 mC, 60 mC







AMYGDALA CHANGES AFTER 6 ECS: Control, 10 mC, 60 mC

- Squares/rectangles: Excitatory synapses
- Circles: Inhibitory synapses
- [Differentiation based on shape circular vs elliptical or flattened]











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AMYGDALA CHANGES AFTER 6 ECS: Control, 10 mC, 60 mC

- Apical dendritic arborization: 60 mC <(10 mC=sham)</p>
- Dendritic nodes: Ditto
- ECS: fewer excitatory, more inhibitory synapses.
- Interpretation
  - High dose ECT may correct the aberrant amygdalar neuroplasticity that mediates fearful affect in depression and PTSD, thereby explaining the efficacy of this treatment in these disorders.
  - High dose ECT may obliterate the fearful affect associated with a stressor without affecting memory of the stressor.



- There is no convincing evidence that ECT induces structural brain damage.
- There is strong evidence that ECT, as clinically practiced, is associated with wide margins of safety in matters such as stimulus parameters and seizure duration.



 There is strong evidence that ECT may be the most potent inducer of neuroplasticity in the brain, reversing the impaired neuroplasticity associated with stress, hypercortisolemia, and depression in critically important brain territories.

## OTHER ACTIONS AND MECHANISMS

- A very large body of literature documents neurotransmitter, neurohormonal, ion channel, electrophysiological, neuroplastic, and other actions of ECT.
- Assembling the jigsaw remains a challenge, much as it does for drug therapy.
- Nevertheless, hypotheses have been constructed, e.g. for antidepressant, anticonvulsant, and amnestic effects.

# ANTICONVULSANT ACTION OF ECT

- Six and 9 (but not 3) ECS increase Kv 7.2 and Kv 11.1 mRNA in the piriform cortex.
- Kv 7.2 mRNA is increased in the hippocampus, as well.
- The increase persists for 7 but not 28 days.
- These potassium channels stabilize membrane potential, regulate neuronal excitability, and may mediate the anticonvulsant action of ECT.
- Hjaresen et al, Br Stim 2012





# NIMHANS RESEARCH: 1

- DA autoreceptors and postsynaptic receptors
- Alpha-2 noradrenergic receptors
- Time-dependent, dose-dependent, rate-ofadministration, duration-of-administration, and maintenance treatment issues
- Antihypertensive and blood-brain barrier breach mechanisms of anterograde and retrograde amnesia

# NIMHANS RESEARCH: 2

 Noradrenergic, nitric oxide, glucocorticoid, and glutamateric mechanisms of amnesia.



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# THANK YOU!

