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

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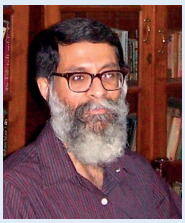

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

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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 is not true. There is a great deal of information available about what ECT does in the brain, how it does it, and how these effects translate into clinical actions. The very complexity of the available data makes it necessary for the question about mechanisms to be properly defined with regard to physiologic effects, adverse effects, and efficacy in different conditions. This article presents a primer for the conceptualization of the mechanism of action of ECT with special attention to understanding why the question and answer are complex.

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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.[1] 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 of the general public, the mass media, nonpsychiatric mental health professionals, and even psychiatrists themselves. A common and unsatisfying response is that the mechanism of action of ECT is unknown but that a seizure is necessary for it to be effective. A proper answer is, however, necessary, because people are used to the idea of taking drugs for the treatment of illness and will accept less-than-satisfying answers to their questions about these drugs; in contrast, they are not used to the idea of electricity being passed through the brain and the induction of a seizure being necessary as a therapeutic measure and so demand a more convincing answer. Before the question is answered, however, the question must be properly defined. The rest of this article will consider this subject.

Defining the Question About How ECT Acts

How does fluoxetine act? The usual answer is that increasing monoamine availability seems to be therapeutic in depression, and fluoxetine increases the availability of the monoamine serotonin by inhibiting the serotonin transporter protein, thereby preventing the reuptake of serotonin from the synaptic cleft.[2] This answer, of course, is simplistic and incomplete for reasons that will soon become apparent. Nevertheless, it appears to satisfy most people, from patients to psychiatrists.

ECT is effective in depression, mania, schizophrenia, and possibly other neuropsychiatric conditions as well.[1] The nub of the situation is that we do not know what causes depression, mania, schizophrenia, and most of the conditions for which ECT has been used. Without a complete understanding of the etiopathogenesis of these neuropsychiatric disorders, it is difficult to determine what action of ECT is therapeutic in what condition. This is a particular problem because ECT produces

Clinical Points

- There is a great deal of information available about the neurotransmitter, neuroendocrine, electrophysiologic, neuroplasticity, and other effects of electroconvulsive therapy (ECT).
- Different actions of different components of ECT treatment explain different acute, subacute, and long-term effects on physiologic, efficacy, and adverse effect outcomes.
- When asking about how ECT acts, it is therefore necessary to know what action of ECT has what specific end result through what specific processes.

a large number of neurobiological effects; it is difficult to determine which effects are relevant and which are epiphenomena for what condition.

This introduces the next problem. As already pointed out, ECT is effective in a variety of dissimilar disorders, some of which are, in fact, conceptually at opposite poles. Approved and experimental indications that are opposites include depression[3] and mania,[4] and Parkinson's disease[5] and tardive dyskinesia.[6] ECT also produces seizures[1] but may be therapeutic in epilepsy.[7] A unitary mechanism should explain the full spectrum of efficacy, that is, across all disorders. It is unlikely, however, that a single explanation can be found for the efficacy of ECT in all of the different approved and experimental indications. Therefore, identification of divergent, disorder-specific mechanisms is needed.

In this context, *where* ECT does what it does might be of guidance; for example, downregulation of neuroplasticity in the amygdala[8,9] versus upregulation of neuroplasticity in the hippocampus[10,11] may explain benefits in posttraumatic stress disorder and depression, respectively.

It is necessary to identify mechanisms that explain physiologic effects of ECT such as on heart rate, blood pressure, and glycemic control,[12] and it is necessary to identify mechanisms that explain the adverse effects of ECT, such as nausea, body ache, and forgetfulness.[12] Furthermore, explanations need to be provided for acute, subacute, and delayed effects. Here, the seizure is an example of an acute effect,[1] tardive seizures may be a subacute effect,[13] and anticonvulsant action is a delayed effect.[7] Again, it is likely that explanations will be divergent rather than unitary.

When considering the different effects of ECT, mechanisms related to the different constituents of the treatment must be considered. In this regard, it is easily understood that the anesthesia could cause the nausea that some patients experience on awakening,[14] that the muscle relaxant (usually succinylcholine) could cause muscle pains,[15] that the anticholinergic drug in the premedication could cause dry mouth and tachycardia,[1,12] and that the electricity itself could be responsible not only for the efficacy but also for adverse effects such as forgetfulness.[1,12]

Returning to an explanation offered at the beginning of this section, why should greater synaptic availability of serotonin explain the mechanism of antidepressant action of fluoxetine? Merely filling a tank with gasoline does not make a car run.[16] It is therefore necessary to identify downstream effects of a treatment, whether the treatment is fluoxetine or ECT. These downstream effects include actions on receptors, intracellular messengers, gene expression, protein synthesis, neuroplasticity changes, and changes in the functioning in different neuronal circuits in the brain. Some of these were reviewed in detail by Fochtmann.[17,18]

Curiosities must be explainable by the models that are proposed. For example, what might explain dramatic response to a single ECT session[19]? Or the development of mania as an adverse effect of ECT *within* a depressive episode[20]? Or, for that matter, what explains treatment resistance?

It would be pleasing if the models proposed were consistent with the suggested mechanisms of action of medications. However, whereas antidepressant drugs and ECT both stimulate neuroplasticity,[16] a hypothesized mechanism of antidepressant action, antipsychotic drugs block dopamine postsynaptic receptors,[2] but ECT upregulates their activity.[21]

There should also be dissonance between models proposed for medications and for ECT, if only to explain why ECT acts faster than drugs, has greater efficacy than drugs in patients with psychotic depression, and often works even after drugs have failed.[1,12]

Interpreting Research Findings

Before explanatory models are proposed, downstream effects and final common pathways may need to be determined. For example, upregulation of dopamine postsynaptic receptors with repeated electroconvulsive shocks in animal models does not necessarily mean increased dopaminergic neurotransmission. This is because the functional status of a pathway depends on synthesis, storage, release, and reuptake of neurotransmitter and on second messenger and other effects distal to the postsynaptic receptors, besides changes in the receptors themselves.

It should also be realized that when a change is demonstrated with ECT, we do not know whether the change is corrective of pathology, compensatory, or merely irrelevant with regard to mechanism of action for a particular outcome.

Finally, most of the research on the mechanism of action of ECT has been conducted on the laboratory rat. Healthy rats belonging to the same strain and reared in a homogeneous environment may respond differently to ECT relative to psychiatrically dysfunctional humans who are heterogeneous in genetic makeup and exposure to environmental influences. Problems in the interpretation of research have been discussed in greater detail elsewhere.[22]

What Was the Question Again?

This article opened with a question about the mechanism of action of ECT. It is evident from the preceding discussion

that the question is quite complex, that the answer is also complex, and that both need to be broken down into many parts. Future articles in this series will continue the discussion on the subject.

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