Mechanism Underlying the Therapeutic Effects of Electroconvulsive Therapy (ECT) on Depression

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ABSTRACT—Electroconvulsive therapy (ECT) is used to treat drug-resistant depressive disorders. The results of studies on the mechanism underlying the effectiveness of ECT on depression are still controversial. ECT stimulus is usually larger than the threshold of induction of seizures and activation of whole-brain is believed to be necessary to produce therapeutic effects. A single ECT session induces alterations of the electroencephalogram (EEG) including initial epileptic discharges, then slow waves, and finally flattened EEG. Repeated ECT results in an increasing number of slower waves in the EEG for as long as a month. ECT-induced changes in various neurotransmitter systems have also been reported. Serotonin (5-hydroxytryptamine, 5-HT) is one of the most important neurotransmitters involved in depressive illness, and ECT alters several 5-HT-receptor subtypes in the central nervous system. 5-HT1A receptors in post-synaptic neurons are sensitized by repeated ECT, but those in pre-synaptic neurons (auto-receptors) are not changed. In addition, our electrophysiological studies have shown that ECT increases sensitivity to 5-HT of 5-HT3 receptors in the hippocampus, resulting in an increase in release of neurotransmitters such as glutamate and γ-aminobutyric acid. In contrast, ECT decreases the auto-receptor functions in noradrenergic and dopaminergic neurons in the locus coeruleus and substantia nigra, respectively, resulting in an increase in release of noradrenaline and dopamine. In conclusion, 5-HT1A-receptor sensitization may be important for explaining the effectiveness of ECT, as this change induces a decrease in the number of 5-HT2A receptors that are elevated in depressive patients. Facilitation of neurotransmitter releases due to 5-HT2-receptor sensitization by ECT may also play an important role in effective treatment of depressive patients refractory to therapeutic drugs.

Keywords: Electroconvulsive therapy (ECT), Serotonin receptor, Depressive disorder

Introduction

Tricyclic antidepressants are potentially effective pharmacotherapy for depressive disorders. Recently, new antidepressants such as selective serotonin re-uptake inhibitors (SSRI) and serotonin-noradrenaline re-uptake inhibitors (SNRI) have been developed (1). However, some depressive patients still remain refractory to such pharmacotherapy. Electroconvulsive therapy (ECT) has been shown to be effective for such retractable depressive disorders. In comparison with SSRI, ECT is still superior in onset and effectiveness on depressive illness (2). In animal experiments to investigate the mechanism underlying the effectiveness of ECT, the term electroconvulsive shock (ECS) is usually used. This paper focuses on serotonergic systems that may underlie the effectiveness of ECT on refractory depression.

Effectiveness of ECT on depressive disorders

ECT is usually performed through electrodes placed on the temporoparietal cranium bilaterally or unilaterally. Effective stimulus strength for ECT is greater than the threshold for inducing either behavioral or electroencephalographic epileptic seizures. Although current density during stimulation is higher in the frontal lobe of the brain or cerebral cortex between the two electrodes in either bilateral or unilateral ECT, currents spread over the whole-brain (3). Therefore, many neurons and neuronal systems are activated and/or affected by ECT. Mean current density of unilateral ECT is about 2/3 that of bilateral ECT. This difference may account for differ-
ences in effectiveness between unilateral and bilateral ECT. Usually bilateral ECT is more effective for depressive disorders than unilateral ECT. Interestingly, bilateral ECT has larger probability for induction of seizure and epileptic discharges than unilateral ECT (4, 5). In addition, changes in brain function in experimental animals with bilateral ECS are larger than those with unilateral ECS. For example, the amount of dopamine released by bilateral ECS is more than unilateral ECS at equal stimulus strengths (6). However, adverse effects of ECT such as amnesia are less with unilateral ECT than bilateral ECT (7). Although single ECT probably changes brain functions, ECT is usually applied repeatedly for therapy of refractory depression, to induce chronic alterations of brain function. Such chronic changes in brain function are probably different from those obtained with single ECT.

Alterations of electroencephalogram (EEG) data recorded during and after ECT have been reported. With a single ECT session, the initial spike and spike-and-wave complex appear in the EEG and then slow waves and/or flattened EEG are observed. Repeated ECT induced an increase in slower waves for as long as a month (8, 9). Changes after subsequent ECT are dependent on the number of sessions. An increase in slow-waves in EEG correlates with the effectiveness of ECT initially after treatment (10). ECT-induced seizures in EEG also appear to be important for therapeutic effectiveness. Thus, the current ECT without convulsion is usually performed under use of an anesthesia and muscle relaxant, monitoring EEG to confirm appearance of seizure discharges.

ECT on serotonergic system

Although a variety of neurotransmitter systems may be affected by ECT in the depressive state, brain monoaminergic systems such as serotonin (5-hydroxytryptamine, 5-HT) are thought to be significantly involved in the therapeutic mechanism of ECT.

Serotonergic neurons located in the dorsal raphe nucleus innervate various regions of the brain to regulate brain functions. Fourteen different 5-HT receptor subtypes have been found in the brain and peripheral tissue (11). Activation of 5-HT_{1A} receptor coupled with G_{i/o} protein decreases cAMP formation in neurons, causing K^+ channel opening and hyperpolarizing membrane potential to decrease neuronal activity in post-synaptic neurons. The 5-HT_{1A} receptor is also found on serotonergic neurons and acts as an auto-receptor to inhibit serotonergic neuron activity (12). In vivo experiments have shown that when repeated sessions of ECS are applied, 5-HT_{1A} receptors on post-synaptic neurons in the hippocampus and forebrain are up-regulated and the 5-HT-induced responses are augmented (13, 14). We have previously demonstrated an enhancement of 5-HT-induced responses via 5-HT_{1A} receptors in hippocampal slices prepared from rats treated with repeated ECS (15). However, 5-HT_{1A}-receptor sensitive reduction of adenylate cyclase activity in the hippocampus has been reported to be attenuated by repeated ECS (16, 17). This suggests that potentiation of electrophysiological response via 5-HT_{1A} receptors is probably mediated by a receptor-effector system of direct coupling of G-protein to K^+ channels. In contrast, 5-HT_{1A} receptors in serotonergic neurons (auto-receptors) are not affected by repeated ECS treatment (18).

5-HT_{3} receptors are coupled with G_{o/s} and activation of the receptor increases turnover of phosphatidylinositol (PI). 5-HT_{3} receptors coupled with G_{i} stimulate cAMP formation. Activation of 5-HT_{3} or 5-HT_{4} receptors induces an increase in excitability of neurons (12), probably by closing K^+ channels. Repeated ECS treatment reportedly increased the number of 5-HT_{3A} receptors in the frontal cortex (19, 20). This phenomena by ECS appears controversial, since an increase in 5-HT_{3A} binding in the frontal cortex of depressive patients has been reportedly observed (21). However, PI turnover by 5-HT agonist through 5-HT_{3} receptors is not changed in the hippocampus (22) and increased in the cortex (23) by repeated ECS treatment. On the contrary, an extended decrease in binding of inositol trisphosphate (IP3) produced by 5-HT_{3} receptor activation has been detected in the hippocampal CA1 region following repeated ECS (24). Furthermore, down-regulation of 5-HT_{3A} receptor functions are reported to be induced by 5-HT_{1A} receptor activation in vivo (25). Therefore, repeated ECT may decrease 5-HT_{3A} receptor functions in depressive patients directly and/or as a result of increasing 5-HT_{1A} receptor function.

5-HT_{3} receptors include cation channels inside the receptors and stimulation of receptors increases neuronal excitability. Activation of 5-HT_{3} receptors depolarizes neurons and increases the release of GABA and/or glutamate in the hippocampus. We have found that 5-HT_{3} receptor functions are augmented in CA1 neurons in the hippocampal slices prepared from rats treated with repeated ECS (26). In agreement with our findings, behavioral studies have shown that the anti-depressive effects of repeated ECS are attenuated by treatment with 5-HT_{3} receptor antagonists (27). In addition to changes in 5-HT receptor function, the number of 5-HT transporters that re-uptake 5-HT into nerve terminals is reported to increase in the frontal cortex with repeated ECS treatment (28). Changes in the serotonergic system with repeated ECS sessions are summarized in Table 1.
Table 1. Effects of repeated ECS on changes of serotonergic system in experiments

<table>
<thead>
<tr>
<th>Pre-synaptic (serotonin)</th>
<th>[Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>turnover</td>
<td>0</td>
</tr>
<tr>
<td>release basal</td>
<td>0</td>
</tr>
<tr>
<td>evoked</td>
<td>↓</td>
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<td>Receptors</td>
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<td></td>
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<td>binding</td>
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<tr>
<td></td>
<td>binding</td>
</tr>
<tr>
<td></td>
<td>↑ (5-HT_{2A}, cortex)</td>
</tr>
<tr>
<td></td>
<td>transporter</td>
</tr>
<tr>
<td>Production of 2nd messengers</td>
<td></td>
</tr>
<tr>
<td>cAMP</td>
<td>↓ (forskolin-induced, 5-HT_{IA})</td>
</tr>
<tr>
<td>IP_{3}</td>
<td>0 or ↑</td>
</tr>
</tbody>
</table>

↑: increase, ↓: decrease, 0: no change, —: not determined.

ECT on other neurotransmitter systems related to affective disorders

Adrenergic and dopaminergic systems are also affected by ECS treatment. The number of $\alpha_2$ receptors in noradrenergic neurons in the locus coeruleus has been reported to be reduced by a single ECS, thereby decreasing auto-receptor function in the neurons (29). These findings suggest that noradrenaline release also increases and enhances stimulation of post-synaptic noradrenergic receptors which are believed to be involved in depressive symptoms.

Functions of dopaminergic receptors (auto-receptor) in dopaminergic neurons in the substantia nigra were also attenuated by ECS. This effect was not dependent on the number of ECS treatments but lasted for several days (29, 30). Reduction of auto-receptor functions resulted in an increase in dopamine release from nerve terminals. An increase in dopamine levels at the synaptic area may also contribute to the anti-depressive effects of ECT. In addition, changes in dopamine receptor mRNA in post-synaptic areas of dopaminergic neurons have been reported in the nucleus accumbens and striatum. In the nucleus accumbens but not in the striatum, single or repeated ECS transiently increased mRNAs for both D_{1} and D_{2} receptors (31). These increases may additionally account for potentiation of dopaminergic functions in treatment of depressive illness.

Possible mechanism of adverse effects of ECT

ECT always produces some memory dysfunction. Memory dysfunction is more pronounced in patients treated with bilateral ECT than those with unilateral ECT (32). ECT-induced amnesia is probably due to a reduction in hippocampal long-term potentiation (LTP) which underlies learning and memory, since in the dentate gyrus, LTP is reduced by repeated ECS treatment (33), although normal synaptic transmission is increased.

Conclusion

In conclusion, the effectiveness of ECT on refractory depression is probably due to alterations in 5-HT-receptor functions, including an increase in the function of 5-HT_{1A} and 5-HT_{3} receptors. Increases in 5-HT_{1A}-receptor function cause a reduction in 5-HT_{2A}-receptor function which is elevated in the frontal cortex of depressive patients. In addition to alterations in 5-HT-subtype receptors, a reduction in dopamine and noradrenaline auto-receptor function, which results in an increase in dopamine and noradrenaline release, may also contribute to the anti-depressive effects of ECT. ECT is also effective in treating mania, schizophrenia and Parkinson’s disease. However, studies on the mechanism underlying the effectiveness of ECT on these diseases are still limited. There are still discrepancies to be solved between effectiveness of ECT on schizophrenic positive symptom and increase in dopamine (D_{1} and D_{2})-receptor levels. Recently, trans-
sccranial magnetic stimulation (TMS) has been found to be an effective method for affective disorders. Further studies on the mechanism responsible for the effectiveness of ECT and TMS may be useful for elucidation of other subtype receptors functions and interaction among neurotransmitters.

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