Electroconvulsive Shock and Neurotransmitter Receptors: Implications for Mechanism of Action and Adverse Effects of Electroconvulsive Therapy

Bernard Lerer

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Abstract

The authors studied the effects of electroconvulsive shock (ECT) on neurotransmitter receptors in the rat brain using radioligand binding techniques. They found that ECT, unlike antidepressant drugs, did not down-regulate receptor densities. ECT did not affect the sensitivity of dopamine receptors to the antipsychotic drug clozapine, but it did increase the sensitivity of noradrenergic receptors to the antidepressant drug clorgyline. The authors concluded that ECT may have therapeutic effects by modulating neurotransmitter receptors.
ECT-induced amnesia. Further studies are needed to critically test the hypothesis that the changes in receptor sensitivity induced by repeated ECS are relevant to the antidepressant action of ECT. Possible parallels between the mechanism of action of ECT and that of lithium are considered. The development of new treatments for mood disorders that are more effective and less controversial than ECT offers promise for the future.

**METHODS**

**ECT and Neurotransmitter Receptors**

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**INTRODUCTION**

ECT is a treatment for depression that has been used for over 50 years. Its mechanism of action is still not fully understood, and its effectiveness is controversial. Recent research has suggested that ECT may act through changes in neurotransmitter receptors, particularly cholinergic receptors.

**ECT and Neurotransmitter Receptors**

Recent research has suggested that ECT may act through changes in neurotransmitter receptors, particularly cholinergic receptors. These changes may be mediated by changes in receptor sensitivity induced by repeated ECS, which in turn may be related to the antidepressant action of ECT. Further studies are needed to confirm this hypothesis and to develop new treatments for mood disorders that are more effective and less controversial than ECT.
Biochemical studies were performed on specimens of rat brain which were rapidly dissected immediately after decapitation. Noradrenaline (NA)-release studies were performed on fresh vesicular preparations on the same day. Tissues for receptor binding studies were frozen at -70°C until assay. All data were analyzed with a Student's t test two-tailed unless otherwise specified.

ECS AND ß-ADRENERGIC RECEPTORS

Down-Regulation of ß-Adrenergic Receptors by Clinically Equivalent ECS

Previous reports had shown that ECS administered daily for 7-10 days induced a significant 25-27% decrease in 3H-dihydroalprenulol (3H-DHA) binding to cortical ß-adrenergic receptors. Bergström and Kellar, 1979; Pandey et al., 1979. This finding was replicated in our studies Birnbaumer et al., 1982 which showed a significant reduction in 3H-DHA binding following daily ECS for 10 days. In the clinical setting, however, ECT is administered according to a spaced schedule 2-3 times per week rather than on a consecutive daily basis. It was therefore of interest to determine whether ECS administered to rats according to a clinically equivalent schedule would induce similar down-regulation of ß-adrenergic receptor number. Rats were administered ECS thrice weekly for 4 weeks and killed 96 hr after the last treatment BeImakher et al., 19821. Cortical ß-adrenergic receptor number was determined by 3H-DHA binding according to the method of Bylund and Snyder 1976.

ECS induced a 21% reduction in ß-adrenergic receptor number (Bmax) with no change in affinity (Kd). This effect was statistically significant and of the same order of magnitude as the change induced by 7-10 daily ECS Bergström and Kellar, 1979; Pandey et al., 1979. It is of interest to note that this finding was demonstrable 4 days after the last ECS. Keller et al., 1981 had reported that following 7 daily ECS, significant down-regulation of ß-adrenergic receptors was still present 7 days after the last treatment. The above finding shows similar persistence of the ECS effect even after a more clinically equivalent schedule. Our studies on the effects of ECS on NA release were directed at exploring the possible role of presynaptic NA mechanisms in mediating the above post-synaptic effects and in the antidepressant action of ECT.

Effect of ECS on NA Release

ECS exerts considerable effects on mechanisms mediating presynaptic NA availability. Repeated ECS has been found to increase NA synthesis and release (Ketv et al., 1967; Modigh, 1976), decrease NA uptake into cortical homogenates (Hendley and Welch, 1975; Minchin et al., 1983), and increase the activity of the rate-limiting enzyme tyrosine hydroxylase (Mussachio et al., 1969). Attenuation of clonidine-induced sedation (Heal et al., 1981), clonidine-induced decrease in brain M50EP-SO4 concentration (Leal et al., 1981), and clonidine-induced hypothermia (Pilc and Vetulani, 1982) have all been demonstrated following repeated ECS. The effects of ECS on presynaptic release were studied by measuring the release of 3H-Na in rat brain cortical homogenates in the presence or absence of clonidine (Ebstein et al., 1983). A gravity-flow perfusion technique recently described by Ebstein et al., 1982 was used.

In the light of these findings, it was of interest to study the effect of repeated ECS on presynaptic release of NA in the presence of clonidine (Ebstein et al., 1982). Chronic monoamine oxidase (MAO) inhibition with clorgyline has recently been shown to increase NA release from a rat brain cortical vesicular preparation and to markedly decrease the inhibition of NA release caused by the selective agonist clonidine (Cohen et al., 1983). Changes in presynaptic release mechanisms may precede and partially mediate postsynaptic reduction in receptor number (Wolfe et al., 1978). We therefore examined the effect of repeated ECS on presynaptic release of NA from a rat brain cortical vesicular preparation in the presence or absence of clonidine (Ebstein et al., 1983).
**Table I.** Effect of Single ECS on K⁺ Evoked[^3]H] Efflux from Rat Cerebral Cortical Vesicular Preparations[^a]

<table>
<thead>
<tr>
<th>CaCl₂ mM</th>
<th>Control</th>
<th>Clonidine nM[^b]</th>
<th>Clonidine nM[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>887 ± 80</td>
<td>538 ± 59**</td>
<td>634 ± 68*</td>
</tr>
<tr>
<td></td>
<td>(15)</td>
<td>(15)</td>
<td>(15)</td>
</tr>
<tr>
<td>0.2</td>
<td>3593 ± 195</td>
<td>2371 ± 174***</td>
<td>2292 ± 181***</td>
</tr>
<tr>
<td></td>
<td>(15)</td>
<td>(15)</td>
<td>(15)</td>
</tr>
</tbody>
</table>

[^a]: The KCl concentration was 18.4 mM. The numbers in parentheses are the number of separate columns measuring [^3]H] efflux in vesicles obtained from ECS and sham-treated animals.

[^b]: Effect of clonidine (50 and 250 nm) on [^3]H] efflux in ECS or Sham groups vs. control [^3]H] efflux in ECS or Sham groups: *p < 0.05, **p < 0.01, ***p < 0.001.

**Table II.** Effect of ECS x 10 on K⁺-Evoked[^3]H] Efflux From Rat Cerebral Cortical Vesicular Preparations[^a]

<table>
<thead>
<tr>
<th>CaCl₂ (mM)</th>
<th>Control</th>
<th>Clonidine nM[^b]</th>
<th>Clonidine nM[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>1350 ± 85[^c]</td>
<td>1071 ± 125[^c]</td>
<td>937 ± 157[^c]*</td>
</tr>
<tr>
<td></td>
<td>(18)</td>
<td>(18)</td>
<td>(18)</td>
</tr>
<tr>
<td>0.2</td>
<td>1614 ± 170</td>
<td>1433 ± 121[^c]</td>
<td>1001 ± 147*</td>
</tr>
<tr>
<td></td>
<td>(17)</td>
<td>(16)</td>
<td>(16)</td>
</tr>
<tr>
<td>1.0</td>
<td>4554 ± 227</td>
<td>3353 ± 207***</td>
<td>3387 ± 234**</td>
</tr>
<tr>
<td></td>
<td>(18)</td>
<td>(18)</td>
<td>(17)</td>
</tr>
</tbody>
</table>

[^a]: The KCl concentration was 18.4 nM. Values are mean ±SEM. Numbers in parentheses are the numbers of separate columns measuring [^3]H] efflux in vesicles obtained from ECS and Sham-treated animals.

[^b]: Effect of clonidine (50 and 250 nM) on [^3]H] efflux in ECS or Sham groups vs. control [^3]H] efflux in ECS or Sham groups: *p < 0.05, **p < 0.01, ***p < 0.001.

The effect of ECS on DA receptors have been studied by the use of in vivo microdialysis.

Clinically Equivalent ECS and DA-Mediated Behaviors

ECS AND DOPAMINE RECEPTORS

The effects of ECS on DA receptors have been studied by the use of in vivo microdialysis.

Prevention of Haloperidol-Induced DA Supersensitivity by ECS

of the DA behaviors tested.

Imidazoline binding sites may be involved in the mediation of the effects of haloperidol on DA behavior. The competition between the imidazoline and dopamine receptor sites for the same binding sites may be mediated by the imidazoline receptors.

Although multiple ECS treatments have been reported to increase DA receptor supersensitivity, the effect of ECS on DA receptor supersensitivity following 7-10 daily ECS has not been studied.

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In vivo microdialysis

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each treatment group was killed by decapitation after the 4-day washout period and the brains removed rapidly. Caudate nuclei were removed by dissection and immediately frozen at -70°C for 3H-spiperone binding assay.

Figure 1 illustrates the results of the behavioral observations. ECS alone did not significantly alter stereotypy scores at any point in the time course. 1-laloperidol pretreatment induced a consistent and highly significant increase in apomorphine-induced stereotypy which was present throughout the 40-mm observation period. Total stereotypy scores (sum of all ten observations) were 36.2 ± 0.9 x SEM for the haloperidol-treated rats and 21.1 ± 1.6 for the control animals (p < 0.001). Administration of ECS concurrently with haloperidol attenuated the haloperidol-induced increase in apomorphine stereotypies, this attenuation becoming more prominent in the last 12 min of the 40-mm observation period. Total stereotypy score for haloperidol plus ECS was 29.0 ± 2.2, which was lower than for haloperidol alone 36.2 ± 0.9 (p < 0.01).

Table III illustrates the results of the 3H-spiperone binding studies. A haloperidol-induced increase in DA receptor number was clearly evident. Concurrent ECS ameliorated the haloperidol-induced supersensitivity as it did in the behavioral experiment. ECS alone induced no changes in dopamine receptor number. There was no difference in the KD for spiperone (mean Kd = 0.75) between the four groups. These findings show ECS effects on changes in DA receptor sensitivity in induced by haloperidol rather than direct effects of ECS on baseline DA receptor function and yielded parallel results with biochemical and behavioral methods. Chronic haloperidol induced a 72% supersensitivity of DA receptors as measured behaviorally, 48% of which was prevented by ECS. The biochemical supersensitivity was 58.2%, 36% of which was prevented by ECS.

These findings demonstrate that ECS effects on changes in DA receptor sensitivity are due to altered DA receptor function rather than direct effects of ECS on baseline DA receptor number. These findings also suggest that ECS may act to attenuate the haloperidol-induced increase in DA receptor sensitivity. The reduction in DA receptor sensitivity in haloperidol-treated rats was mediated by ECS, which prevented the increase in DA receptor sensitivity induced by haloperidol.

Table III. Effect of ECS on Haloperidol-Induced DA Sensitivity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Umax (pmol/mg)</th>
<th>Kd (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.75 ± 0.05</td>
<td>0.73 ± 0.07</td>
</tr>
<tr>
<td>Haloperidol + ECS</td>
<td>0.84 ± 0.06</td>
<td>0.73 ± 0.07</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.31 ± 0.04</td>
<td>0.73 ± 0.07</td>
</tr>
<tr>
<td>ECS alone</td>
<td>0.59 ± 0.05</td>
<td>0.73 ± 0.07</td>
</tr>
</tbody>
</table>

Relevance to Mechanism of Action of ECT and Lithium

ECT and Lithium share a similar therapeutic profile characterized by a unique bidirectional clinical efficacy in affective disorders. ECT is a treatment of choice for severe depressions and has been effective in mania and may have prophylactic efficacy for recurrent affective episodes. Lithium is uniquely antimanic, possibly antidepressant, and highly effective in preventing affective decompensation in patients with bipolar disorder and possibly unipolar patients.

Preliminary findings suggest that ECS may act to attenuate the haloperidol-induced increase in DA receptor sensitivity. These findings provide a basis for further investigation of ECS as a treatment for affective disorders.
This effect is transient, however, and no longer detectable after a series of
ECS applications to increase dopamine turnover, as shown by a decrease in
3H-spiperone binding. 3. Rosenblatt et al. (1980) have suggested that ECS may
in fact induce a partial down-regulation of DA receptors which may be
mechanistically relevant to the prophylactic action of both treatments.

**Presynaptic Cholinergic Effects of ECS**

**ECS AND ACETYLCHOLINE RECEPTORS**

The findings reported above suggest a parallel effect of ECS on H-z receptor
binding in the hippocampus. This raises the possibility that ECS may
influence the binding of H-z receptors by activating cholinergic system.

In contrast to ECS, Li has little or no direct effect on these receptors. This
suggests that the effects of ECS and Li may be mediated through different
mechanisms. Further studies are needed to elucidate the role of ECS in
regulating H-z receptor binding.

**References**

1. Rosenblatt et al. (1980) have suggested that ECS may induce a
partial down-regulation of DA receptors which may be
mechanistically relevant to the prophylactic action of both treatments.

2. The finding that concurrently administered Li prevents behavioral DA
supersensitivity in animals treated with ECS is consistent with the
idea that ECS may stabilize receptor sensitivity. However, the
mechanism of this stabilization remains to be elucidated.

3. Rosenblatt et al. (1980) have suggested that ECS may
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supersensitivity in animals treated with ECS is consistent with the
idea that ECS may stabilize receptor sensitivity. However, the
mechanism of this stabilization remains to be elucidated.

5. Further studies are needed to elucidate the role of ECS in
regulating H-z receptor binding.
and revealed a dose-dependent decrease in high-affinity choline uptake which did not significantly differ between 20-40 mg/kg atropine alone and 20-40 mg/kg atropine concurrent with ECS in this study.

**Down-Regulation of Muscarinic Cholinergic Receptors by ECS**

ECS-induced changes in high-affinity choline uptake and choline release are consistent with a down-regulation of muscarinic cholinergic receptors. The prevention by concurrent ECS of atropine-induced supersensitivity further supports this concept.

**Table IV. Effect of Single and Repeated ECS on Muscarinic Cholinergic Receptors in Rat Cerebral Cortex and Hippocampus**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cortex</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECS X 1</td>
<td>108 ± 5.8%</td>
<td>95 ± 5.8%</td>
</tr>
<tr>
<td>ECS X 7</td>
<td>85 ± 4.4%</td>
<td>103 ± 4.1%</td>
</tr>
<tr>
<td>24 hr after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECS X 1</td>
<td>96 ± 10.0%</td>
<td>87 ± 4.7%</td>
</tr>
<tr>
<td>ECS X 7</td>
<td>85 ± 4.4%</td>
<td>96 ± 5.8%</td>
</tr>
<tr>
<td>7 days after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECS X 1</td>
<td>103 ± 4.1%</td>
<td>95 ± 5.8%</td>
</tr>
<tr>
<td>ECS X 7</td>
<td>85 ± 4.4%</td>
<td>96 ± 5.8%</td>
</tr>
</tbody>
</table>

The prevention of atropine-induced supersensitivity by ECS indicates that ECS-induced changes in high-affinity choline uptake and choline release are consistent with a down-regulation of muscarinic cholinergic receptors.
Relevance to Antidepressant Mechanism of ECT

Reduction of muscarinic cholinergic receptor density by chronic ECS may be functionally related to the antidepressant efficacy of ECT. This possibility may be considered in the light of theories linking depression to cholinergic predominance (Janowsky et al., 1972) as well as more recent findings of "super sensitivitv" of cholinergically mediated REM sleep induction (Sitarani and Gillin, 1981) and increased fibroblast 3H-QNB binding sites (Nadi et al., 1980) and increased hippocampal 3H-QNB binding sites (Nadi et al., 1980). Lithium, by increasing neuronal firing and enhancing the firing of cholinergic neurons, may have a role in the antidepressant action of ECT by increasing cholinergic neurotransmission. The possibility that chronic ECS reduces cortical cholinergic receptor density may be relevant to the antidepressant effect of ECT by chronically reducing cholinergic neurotransmission.

Recent advances in determining the role of cholinergic mechanisms in the pathogenesis of depression have led to the hypothesis that chronic ECS reduces muscarinic cholinergic receptor density in the cerebral cortex. This reduction in receptor density may be functionally related to the antidepressant efficacy of ECT. The reduced receptor density may be related to the reduced firing of cholinergic neurons and the reduced ability of these neurons to release acetylcholine. The reduced acetylcholine release may be related to the decreased firing of these neurons and the decreased ability of these neurons to release acetylcholine. The reduced acetylcholine release may be related to the decreased firing of these neurons and the decreased ability of these neurons to release acetylcholine.
A hypothesis linking ECT-induced amnesia to alterations in brain cholinergic function could represent an important heuristic step in further unraveling the role of acetylcholine in memory processes. Studies aimed at testing the cholinergic hypothesis of ECT-induced amnesia in humans, as well as in rodents, should improve it as in patients with Alzheimer's disease. Antagonists to ECT-induced amnesia but also to the wider spectrum of memory disorders in depression of ECT and adverse effects. The number of implications for previously suggested mechanisms and newer approaches to ECT-induced amnesia derived from studies on ECS effects in "normal" rats and other neurological and pharmacological preparations. Further basic studies are clearly needed in order to advance the putative antidepressant and adverse mechanisms of ECT outlined here. Further clinical studies evaluating effects of ECS in parallel with those of other effective antidepressant treatments represent a potentially fruitful approach.

CONCLUSIONS

The effects of ECS on the cholinergic and other neurotransmitter-receptor systems have been shown to influence memory processes. The number of ECS-induced changes in the brain, particularly in cholinergic function, may play a role in the development of depression.

REFERENCES

ACKNOWLEDGMENTS

This hypothesis may be tested both clinically and in the laboratory. The number of ECS-induced changes in the brain, particularly in cholinergic function, may play a role in the development of depression.

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