ELECTROCONVULSIVE SHOCK INCREASES THE BEHAVIOURAL RESPONSES OF RATS TO BRAIN 5-HYDROXYTRYPTAMINE ACCUMULATION AND CENTRAL NERVOUS SYSTEM STIMULANT DRUGS

JANE P.M. EVANS, D.G. GRAHAME-SMITH, A.R. GREEN & ANN F.C. TORDOFF

MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE

1 A single electroconvulsive shock (ECS) of 150 V for 1 s increased the concentration of rat brain 5-hydroxyindoleacetic acid (5-HIAA) but did not alter brain 5-hydroxytryptamine (5-HT) or tryptophan concentrations 3 h later.

2 A single ECS decreased 5-HT synthesis 3 h and 6 h later. Synthesis was back to normal after 24 hours. The ECS-treated rats did not show greater hyperactivity produced by the increased brain 5-HT accumulation following administration of L-tryptophan and tranlycypromine at any time up to 24 h later. This suggests that a single electroshock does not alter 5-HT functional activity.

3 Twenty-four hours after the final ECS of a series of 10 shocks given once daily, the rats were given tranlycypromine and L-tryptophan. They displayed greater hyperactivity than control rats not treated with ECS, suggesting that ECS increased 5-HT functional activity. Brain concentrations of 5-HT, 5-HIAA and tryptophan were then unchanged by ECS. 5-HT synthesis and accumulation of 5-HT following tranlycypromine and L-tryptophan were not altered by ECS.

4 The hyperactivity following administration of the 5-HT agonist 5-methoxy *N,N*-dimethyltryptamine was enhanced by repeated (10 day) ECS, suggesting altered post-synaptic responses to 5-HT receptor stimulation.

5 Repeated ECS enhanced locomotor activity following tranlycypromine and L-DOPA. It did not alter brain noradrenaline or dopamine concentrations.

6 The latent period before a pentylenetetrazol-induced convulsion was shortened by repeated ECS.

7 Following repeated ECS there appears to be increased neuronal sensitivity to certain stimuli producing centrally mediated behavioural stimulation. This is discussed in relation to the mechanism by which electroconvulsive therapy (ECT) produces its therapeutic effect.

Introduction

Despite the fact that electroconvulsive therapy (ECT) has been extensively used for many years to treat psychiatric illness, the mechanism of its action is unknown. Reports on the effect of electroconvulsive shock (ECS) on the biogenic amines of rat brain are contradictory both after single and multiple shocks (Essman, 1973).

We have recently developed a behavioural model to study changes in the metabolism and functional activity of 5-hydroxytryptamine (5-HT) in rat brain (Green & Grahame-Smith, 1975a). This has now been used to study the effects of short and long-term ECS on the functional activity of this amine in rat brain. The effects of ECS on brain 5-HT synthesis and metabolism have also been examined.

Methods

Male Sprague-Dawley rats weighing 150–220 g (Anglia Laboratory Animals, Alconbury, Huntingdon) were used in all experiments. They were housed in groups of 3 and given small animal 41B diet and tap water *ad libitum* for the duration of the experiment.

All drugs were dissolved in 0.9% w/v NaCl solution (saline) or suspended in 1% carboxymethylcellulose in saline and given intraperitoneally. Drugs were obtained from the following sources: L-tryptophan, L-DOPA, 5-methoxy-*N,N*-dimethyltryptamine and pentylenetetrazol (Sigma Chemical Company) and tranlycypromine (S.K.&F.).

Electroconvulsive shocks were applied through ear-clip electrodes from an Edison portable ECT unit.

Shocks (50 cycle/s sinusoidal, 150 V for 1 s) were given to rats lightly anaesthetized with halothane. Control rats were anaesthetized but received no electroconvulsive shocks.

Brain 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations were measured by the method of Curzon & Green (1970), tryptophan by that of Denckla & Dewey (1967) and dopamine and noradrenaline by the method of Chang (1964). Brain 5-HT synthesis was determined by the method of 5-HT accumulation following monoamine oxidase (MAO) inhibition as described by Neff & Tozer (1968). Activity was measured on groups of 3 animals with Animex activity meters (sensitivity and tuning: 30 μ A) as described previously (Grahame-Smith, 1971a; Green & Grahame-Smith, 1974a). Graphs show results of typical experiments performed at least twice.

Results

Effect of a single electroshock on rat brain 5-hydroxytryptamine, 5-hydroxyindoleacetic acid and tryptophan concentrations

Groups of rats were anaesthetized and given either a single shock or no shock. They were killed either 30 min or 180 min later and brain 5-HT and 5-HIAA determined. No change in the concentration of either compound was observed 30 min after treatment. However, 3 h after treatment the ECS group had a higher concentration of 5-HIAA although 5-HT concentrations were unchanged (Table 1).

No evidence was obtained for any alteration of brain tryptophan concentrations following a single ECS (Table 1).

Effect of a single ECS on brain 5-hydroxytryptamine synthesis at various times after the shock

Shields (1972) and Tagliamonte, Tagliamonte, Di Chiara, Gessa & Gessa (1972) found brain 5-HIAA increased following a single ECS but 5-HT synthesis rates were not studied. The rate of 5-HT synthesis at

various times after a single electroshock was therefore examined by measuring the rate of 5-HT accumulation following tranylcypromine.

Groups of rats were anaesthetized and given a single electroshock or no shock. One, 3, 6 and 24 h later both groups were given tranylcypromine (20 mg/kg) and the rate of 5-HT accumulation measured 60 min later. Anaesthesia did not alter the rate of 5-HT synthesis at any time as judged by the rate of 5-HT accumulation following tranylcypromine administration to untreated rats (Table 2). However, the rate of 5-HT synthesis was decreased significantly 3 and 6 h after a single electroshock. The rate had returned to normal by 24 h (Table 2).

Effect of ECS on the hyperactivity following tranylcypromine and L-tryptophan administration

To see whether the functional activity of rat brain 5-HT was altered by ECS we examined the effect of a single electroshock on the behavioural response to tranylcypromine and L-tryptophan administration, a procedure which increases 5-HT synthesis and its 'spill-over' into functional activity in the brain (Grahame-Smith, 1971a; Grahame-Smith, 1973). Previously, it has been shown that compounds altering 5-HT compartmentation and release, re-uptake or post-synaptic responses in the brain will cause alterations in the hyperactivity following administration of tranylcypromine and L-tryptophan (for review see Green & Grahame-Smith, 1975a).

Rats were anaesthetized and then given a single ECS or no shock. One, 3, 6 and 24 h later both groups were given tranylcypromine (20 mg/kg) followed 30 min later by L-tryptophan (100 mg/kg) and activity measured. No difference in the hyperactivity response to tranylcypromine and L-tryptophan was observed between the groups at any time.

Effect of ECS given once daily for 10 days on rat brain tryptophan, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid concentrations and the rate of 5-hydroxytryptamine synthesis

Since no behavioural changes were observed after one electroshock the effects of a single ECS given daily for

Table 1 Effect of single electroconvulsive shock (ECS) on rat brain 5-hydroxytryptamine (5-HT) 5-hydroxyindoleacetic acid (5-HIAA) and tryptophan 3 h later

Treatment	Brain concentrations in μ g/g brain (wet wt)		
	5-HT	5-HIAA	Tryptophan
Control	0.38 $\pm$ 0.01 (14)	0.23 $\pm$ 0.01 (14)	2.19 $\pm$ 0.19 (5)
ECS	0.38 $\pm$ 0.02 (13)	0.27 $\pm$ 0.01 (14)*	1.86 $\pm$ 0.12 (6)

Results expressed as mean $\pm$ s.e. mean. No. of observations in brackets.

* Different from anaesthetized control $P < 0.01$

10 days was examined. Rats were anaesthetized and given a single shock or no shock at the same time of day (12 h 30 min–13 h 30 min) for 10 days. Twenty-four hours after the final shock both groups were killed and brain tryptophan, 5-HT and 5-HIAA concentrations measured. A further ECS treated group received tranlycypromine (20 mg/kg) and 5-HT accumulation was measured 1 h later. There was no change following repeated ECS in the concentration of 5-HT, 5-HIAA or tryptophan in the brain. Nor was any change observed in the rate of 5-HT synthesis (Table 3).

Effect of repeated ECS on the hyperactivity following tranlycypromine and L-tryptophan

Rats were anaesthetized and given a single shock or no shock for 10 days as described above. Twenty-four

hours after the final treatment both groups were given tranlycypromine (20 mg/kg) followed 30 min later by L-tryptophan (50 mg/kg). Activity was measured simultaneously on both groups. Following tranlycypromine the ECS-treated rats showed a small but consistently greater amount of locomotor activity than the control group (approximately 30 movements/min or more). When tryptophan was administered both groups displayed the characteristic syndrome of hyperactivity previously reported following this treatment (Grahame-Smith, 1971a). However, the ECS-treated group was more active than the control and the hyperactivity also started earlier in this group. This was true even when the initially greater activity following tranlycypromine was subtracted from the results (Figure 1).

There was no difference between the groups in the rate of brain 5-HT accumulation 90 min after L-

Table 2 Effect of a single electroconvulsive shock (ECS) on rat brain 5-hydroxytryptamine (5-HT) synthesis at various times after the shock

Treatment	Time after treatment (h)	Brain 5-hydroxytryptamine conc μg 5-HT/g brain (wet wt)		Rate of 5-hydroxytryptamine synthesis ($\mu\text{g g}^{-1} \text{h}^{-1}$)
		Saline	Tranlycypromine (20 mg/kg)	
Untreated	—	0.41 ± 0.03 (6)	0.60 ± 0.03 (4)	0.19
Control	1	0.34 ± 0.06 (5)	0.58 ± 0.02 (3)	0.24
ECS	1	0.38 ± 0.08 (5)	0.59 ± 0.01 (5)	0.21
Control	3	0.38 ± 0.01 (14)	0.56 ± 0.02 (6)	0.18
ECS	3	0.38 ± 0.02 (13)	0.50 ± 0.02 (9)*	0.12
Control	6	0.35 ± 0.04 (3)	0.57 ± 0.03 (6)	0.22
ECS	6	0.37 ± 0.03 (3)	0.49 ± 0.01 (7)*	0.12
Control	24	0.38 ± 0.02 (3)	0.58 ± 0.03 (3)	0.20
ECS	24	0.37 ± 0.02 (3)	0.57 ± 0.02 (4)	0.20

Results are expressed as mean $\pm$ s.e. mean with number of observations in brackets. Rate of synthesis calculated by determination of the accumulation of 5-HT 1 h after tranlycypromine (20 mg/kg).

* Different from control, $P < 0.01$.

Table 3 Effect of daily electroconvulsive shock (ECS) for 10 days on the concentration of rat brain tryptophan, 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA) and the rate of 5-HT synthesis 24 h after the final shock

Treatment	Brain concentrations in $\mu\text{g/g}$ brain (wet wt)			5-HT conc 60 min after tranlycypromine (20 mg/kg)	Rate of 5-HT synthesis ($\mu\text{g g}^{-1} \text{h}^{-1}$)
	Tryptophan	5-HIAA	5-HT		
Control	1.88 ± 0.07 (5)	0.29 ± 0.01 (5)	0.38 ± 0.04 (5)	0.65 ± 0.03 (6)	0.27
ECS	2.05 ± 0.05 (4)	0.29 ± 0.01 (4)	0.37 ± 0.02 (4)	0.62 ± 0.04 (5)	0.25

Results expressed as mean $\pm$ s.e. mean with number of observations in brackets. Rate of 5-HT synthesis determined by measuring rate of 5-HT accumulation 1 h after inhibition of MAO by tranlycypromine (20 mg/kg).

Figure 1 Effect of repeated ECS on the hyperactivity following tranylcypromine and L-tryptophan. Rats were given a single ECS each day for 10 days. Twenty-four hours after the final shock they were injected with tranylcypromine (20 mg/kg) and L-tryptophan (50 mg/kg) 30 min later. Figure shows the hyperactivity following the tryptophan in the control (halothane anaesthesia only) group (■) and the ECS group (□). For experimental details see methods section.

tryptophan administration (control group: 0.81 ± 0.04 ($n=6$); ECS group: 0.82 ± 0.06 ($n=6$) 90 min after L-tryptophan administration).

Effect of repeated ECS on the hyperactivity following tranylcypromine and 5-methoxy N,N-dimethyl-tryptamine

Since there were no apparent differences in the metabolism of brain 5-HT in the control and experimental groups to explain the enhanced response to 5-HT release it seemed possible that there was a change in the post-synaptic response to the released transmitter. This was tested indirectly with the 5-HT analogue 5-methoxy N,N-dimethyltryptamine (5-MeODMT). It has been suggested that this compound directly stimulates post-synaptic 5-HT receptors allowing observation to be made of changes occurring at the receptor site or in the activity of neural systems beyond this involved in producing the complete behavioural response (Grahame-Smith, 1971b).

Rats were given ECS for 10 days as described above. Twenty-four hours after the final shock both groups were injected with tranylcypromine (20 mg/kg) and with 5-MeODMT (2 mg/kg) given 30 min later. The ECS-treated group did not show any increase in the peak activity after this dose of 5-MeODMT but the activity was more prolonged (Figure 2). When a lower dose of 5-MeODMT was used (1 mg/kg) the ECS-treated group showed both a

greater peak activity and subsequent enhanced activity compared to the control group. This suggests an increased post-synaptic response to stimulation.

Effect of repeated ECS on the hyperactivity following tranylcypromine and L-DOPA

Previously it has been shown that the hyperactivity resulting from increased 5-HT receptor stimulation is dependent upon adequate brain dopamine concentrations and it appeared that the dopaminergic system involved lies at some point between the 5-HT neurones initiating the response and the total neuronal mechanisms responsible for the expression of the hyperactivity syndrome (Green & Grahame-Smith, 1974a). In order to see whether the presumed increased post-synaptic responses to 5-HT activity after repeated ECS was mediated through changes in this dopaminergic system we investigated the effect of repeated ECS on the locomotor stimulation following tranylcypromine and L-DOPA. This hyperactivity is not identical to that following tranylcypromine and tryptophan. It can nevertheless be measured on activity meters.

Rats were shocked for 10 days as described above. Twenty-four hours after the final shock they were injected with tranylcypromine (20 mg/kg) followed 30 min later by L-DOPA (50 mg/kg).

Rats given ECS showed much more activity than control animals (Figure 3). No evidence was found for

Figure 2 Effect of repeated electroconvulsive shock (ECS) on the hyperactivity following tranylcypromine and 5-methoxy *N,N*-dimethyltryptamine (5-MeODMT). Rats were given a single ECS each day for 10 days. Twenty-four hours after the final shock they were injected with tranylcypromine (20 mg/kg) and with 5-MeODMT (2 mg/kg) 30 min later. Figure shows the hyperactivity following the 5-MeODMT in the control (halothane anaesthesia only) group (■) and the ECS group (□). For experimental details see methods section.

changes in the steady state concentration of brain dopamine or noradrenaline in rats treated with ECS for 10 days.

Effect of a single ECS on the hyperactivity following tranylcypromine and L-DOPA 10 days later

To see whether the enhanced response to tranylcypromine and L-DOPA following repeated electroshock was due to the repeated shocks or because of a changed response present 10 days after the first shock, we gave a single shock to a group of rats on day 1 and challenged them with tranylcypromine (20 mg/kg) and L-DOPA (50 mg/kg) as described above on day 11. No difference in locomotor activity was observed between the control and single ECS-treated groups.

Effect of repeated ECS on the latent period before convulsion following pentylentetrazol administration

Because ECS enhanced the behavioural changes due to increases in brain 5-HT and dopamine we decided

Figure 3 Effect of repeated electroconvulsive shock (ECS) on the hyperactivity following tranylcypromine and L-DOPA. Rats were given a single ECS each day for 10 days. Twenty-four hours after the final shock they were injected with tranylcypromine (20 mg/kg) and with L-DOPA (50 mg/kg) 30 min later. Figure shows the hyperactivity following the L-DOPA in the control (halothane anaesthesia only) group (■) and the ECS group (□). For experimental details see methods section.

to see whether it was altering neuronal sensitivity more generally. This was done by examining the effect of repeated ECS on the time taken for rats to convulse following pentylentetrazol administration.

Rats were shocked for 10 days as described earlier. Twenty-four hours after the last shock they were given pentylentetrazol (80 mg/kg) and the time taken

Table 4 Effect of electroconvulsive shock (ECS) on length of latent period before pentylentetrazol-induced convulsions

Treatment	Time (s) after pentylentetrazol before first convulsion
Control	345 ± 152 (5)
ECS	75 ± 16 (5)*

Rats were anaesthetized and given a single ECS or no shock (control) for 10 days. On day 11 both groups were given pentylentetrazol (80 mg/kg) and the time until the first convulsion measured. Results expressed as mean ± s.e. mean of time taken to convulse. Significance calculated using Mann-Whitney non-parametric statistics (Snedecor & Cochran, 1967).

* $P < 0.01$.

between injection and convulsion measured. The group treated with ECS convulsed after a shorter latent period than the control animals (Table 4).

Discussion

Both Shields (1972) and Tagliamonte *et al.* (1972) found an increased brain 5-HIAA concentration 3 h after a single ECS. We have confirmed this and like Shields (1972) are unable to find the concomitant rise of brain tryptophan reported by Tagliamonte *et al.* (1972).

Measurement of brain 5-HT turnover, far from showing an increase, indicated clearly that 5-HT synthesis is decreased approximately 50% both 3 h and 6 h after the shock. Since electrical stimulation of brain slices leads to a release of 5-HT from its stores (Chase, Breese & Kopin, 1967), ECS might produce similar changes *in vivo* leading to an increased concentration in the synaptic cleft, following which it is metabolized by MAO producing the transient 5-HIAA increase. This postulated increase in synaptic cleft concentration of the transmitter would be expected to cause an increased stimulation of the receptor (Meek, Fuxe & Andén, 1970; Modigh, 1973a) and a decrease in the rate of 5-HT synthesis (Meek & Werdinius, 1970; Green & Grahame-Smith, 1975b) probably because increased receptor stimulation causes a 'feedback inhibition' of synthesis, possibly via an action on nerve impulse flow (Modigh, 1973b).

The fact that a single ECS had no effect on the hyperactivity response following tranlycypromine and L-tryptophan suggests that one ECS does not affect the functional activity of 5-HT (for review see Green & Grahame-Smith, 1975a). After 10 days of repeated ECS, however, there was considerable enhancement of the hyperactivity following tranlycypromine and tryptophan. Twenty-four hours after the last ECS of 10 daily shocks there was no change in the steady state concentration of brain tryptophan, 5-HT, 5-HIAA or the synthesis rate of 5-HT to account for this change. It seemed possible therefore that the increased hyperactivity was due to an alteration of the post-synaptic response to stimulation by 5-HT. This was confirmed by the observation that ECS enhanced the hyperactivity response to the 5-HT agonist 5-MeODMT which probably stimulates post-synaptic 5-HT receptors (Grahame-Smith, 1971b).

The activity following tranlycypromine and L-DOPA was considerably enhanced by ECS, although ECS did not alter the steady state concentration of dopamine or noradrenaline. This result suggests that ECS alters post-synaptic responses of the dopaminergic systems in the brain. Modigh (1975) also recently reported that repeated but not single ECS to mice leads to enhanced catecholaminergic post-synaptic sensitivity and our results are in accord with this interpretation, although they suggest that the 5-hydroxytryptaminergic system may have been similarly altered. However, in view of the proposed involvement of dopaminergic system in the production of the hyperactivity resultant upon increased brain 5-HT accumulation (Green & Grahame-Smith, 1974a) it is not clear whether this alteration is due solely to changes in the dopaminergic system.

Similar alterations in hyperactivity without observable biochemical changes were seen in a previous study of Thyrotrophin Releasing Hormone (TRH) (Green & Grahame-Smith, 1974b). TRH appears to alter neuronal sensitivity to certain pharmacological stimuli. Both repeated ECS and TRH shortened the latent period before pentylene-tetrazol-induced convulsions, suggesting that ECS also alters neuronal sensitivity more generally in the brain than just to the amine neurotransmitters. This striking similarity between the effect of TRH and repeated ECS tempts us to propose a unitary mode of action since it has been previously suggested that certain brain polypeptides or proteins with a short biological half life were involved in mediating or modulating neuronal responses to central monoamine activity (Grahame-Smith, 1972; Green & Grahame-Smith, 1975a). ECS might result in the greater production of these polypeptides or proteins, or in their increased effect. The hypothesis might also explain the effects of ECS on animal behaviour which may be analogous with the therapeutic effects of repeated ECT in man. Tricyclic anti-depressants and monoamine oxidase inhibitors (with or without tryptophan) are thought to act by increasing monoamine concentrations in the synaptic cleft, resulting in greater stimulation of the post-synaptic receptor site. In contrast, ECT appears to be working by increasing the post-synaptic responses to the stimulation of the post-synaptic receptor site.

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