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Spaced electroconvulsive treatment: effects on responses associated with α_2- and 5-HT_2-receptors

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We have recently found in animal studies that chronic electroconvulsive treatment (ECT) produces changes suggesting down-regulation of α_2 adrenoceptors (Pilc & Vetulani 1982b) and up-regulation of 5-HT_2 receptors (Vetulani et al 1981). In those studies, as in several other animal experiments, ECT was administered at 24 h intervals. However, in the clinic, ECT is almost always given less frequently, preferably at 3 day intervals (Kiloh 1977). The present experiment was designed to test if the electroshock administered in a manner more closely resembling the clinical situation will also produce the characteristic changes in responsiveness of the systems associated with α_2 and 5-HT_2 receptors.

Materials and methods

Male Wistar rats, 190–230 g, were kept ten to a cage and allowed free access to water and granulated laboratory diet. Electroshocks were effected by passing electric current (150 mA, 50 s^{-1}, 400 ms) through ear clip electrodes; this invariably produced clonic seizures. The rats received either a single shock, or 2 shocks 9 days apart, or a series of more frequent shocks, up to a daily treatment for 10 days, as indicated in the Tables. The tests or decapitations were carried out 24 h after the last shock, and the experiments were scheduled in this manner so that, for a given test, all groups receiving ECT by the various schedules were tested on the same day.

Clonidine-induced hypothermia was defined as the difference in oesophagal temperatures (measured with an Ellab electric thermometer) before and 60 min after the injection of 100 μg kg^{-1} of clonidine hydrochloride (Boehringer) intraperitoneally. At this time the depression of body temperature by clonidine in the rat is most pronounced (Pilc & Vetulani 1982a).

Head twitch response to 5-hydroxytryptamine (5-HT)-mimetics was induced either by intraventricular injection of 250 μg 5-HTP (DL-5-hydroxytryptophan; Sigma) dissolved in 20 μl of 0·9% NaCl (saline) to rats pretreated 30 min earlier with tranylcypromine hydrochloride (Sigma), 20 mg kg^{-1}; or by intraperitoneal injection of 10 mg kg^{-1} quipazine. The intraventricular injection was given to non-anaesthetized rats by a free-hand, direct brain puncture technique (Vetulani et al 1972). Head twitch episodes were counted six times during 4 min periods at 10 min intervals (Corne et al 1963), and presented as mean frequency of episodes per hour.

* Correspondence.

Radioligand binding assay was carried out on the membranes from the whole cerebral cortex ([^{3}H]clonidine) or frontal cortex ([^{3}H]spiperone) as described earlier (Pilc & Vetulani 1982a,b; Vetulani et al 1981).

Statistical analysis of results was carried out with the analysis of variance; specific comparisons were made using the Duncan test.

Results

Hypothermia induced by clonidine was significanly attenuated in rats receiving 4 electroshocks at 72 h intervals; a similar (although less marked) effect was observed in the rats receiving ECT more often and more frequently, while less frequent treatment did not produce an effect significantly different from the control value (Table 1).

Head twitch response produced by 5-HT-mimetics was significantly augmented not only in the rats receiving ECT on the daily basis, but also in those receiving it less frequently, even at 4 (but not 5) day intervals. Quipazine produced a similar effect, so that all groups displayed increased responsiveness to the drug, while 5-HTP acted more strongly in the group treated daily than in the remaining groups.

Receptor binding studies indicated a significant depression of [^{3}H]clonidine binding sites not only in the group receiving daily treatment, but also in that receiving ECT at 3 day intervals, and there was a significant increase in [^{3}H]spiperone binding to the membranes of both groups receiving repeated ECT. Under the experimental conditions [^{3}H]spiperone labels 5HT_2 binding sites (Peroutka & Snyder 1979).

Discussion

Early studies on the mode of action of antidepressant drugs suffered from the discrepancy between laboratory

Table 1. The effect of various ECT schedules on hypothermic response to clonidine.

ECT		Clonidine hypothermia	
Number	Spacing (h)	Mean ± s.e.m. (°C) (°C)	Percent of control
0	(Control)	−3·23 ± 0·12 (10)	100
1	—	−2·93 ± 0·21 (10)	91
3	120	−2·63 ± 0·19 (9)	81
3	96	−3·29 ± 0·15 (10)	102
4	72	−0·89 ± 0·51 (10)	28**
5	48	−1·65 ± 0·39 (9)	51*
10	24	−1·97 ± 0·16 (10)	61*

F = 9·33 (6/61). Difference from control: *$P<0·05$, ** $P<0·01$ (Duncan test).

Table 2. The effect of various ECT schedules on head twitch response to 5-HT-mimetics.

ECT		Head twitch frequency (h^{-1})			
		after 5-HTP, 250 μg i.v.c.		after quipazine, 5 mg kg^{-1}	
Number	Spacing (h)	Mean ± s.e.m. (n)	% control	Mean ± s.e.m. (n)	% control
1	(control)	136 ± 5 (7)	100	124 ± 2 (9)	100
2	216	132 ± 5 (9)	97	134 ± 5 (7)	104
3	120	135 ± 3 (8)	99	137 ± 3 (7)	106
3	96	168 ± 5 (7)	123**	162 ± 6 (8)	125**
4	72	168 ± 5 (8)	123**	161 ± 6 (8)	125**
5	48	192 ± 6 (7)	141**	170 ± 4 (7)	131**
10	24	238 ± 6 (7)	175**	169 ± 4 (8)	131**
		F = 54·2 (6/46)		F = 13·8 (6/47)	

** $P<0·01$ (difference from control), $P<0·01$ (difference from all other groups).
Rats given 5-HTP were pretreated 30 min earlier with tranylcypromine, 20 mg kg^{-1} i.p.

Table 3. The effect of various ECT schedules on [^{3}]clonidine and [^{3}H]spiperone binding to the membranes from cerebral cortex of the rat.

ECT		Specific binding (fmol/mg protein)			
		3nM [^{3}H]clonidine		0·9nM [^{3}H]spiperone[a]	
Number	Spacing (h)	Mean ± s.e.m. (n)	% control	Mean ± s.e.m. (n)	% control
0	(control)	51·2 ± 1·4 (4)	100	17·4 ± 0·9 (4)	100
1	—	48·7 ± 1·5 (4)	97	16·6 ± 0·5 (4)	95
5	72	45·4 ± 1·9 (4)	89*	23·5 ± 1·0 (4)	135**
10	24	36·7 ± 1·3 (4)	72**	20·4 ± 0·7 (4)	117*

[a] Binding to membranes from the frontal cortex.
* $P<0·05$, ** $P<0·01$ (difference from control, Duncan test) Membrane preparations were prepared as described previously (Vetulani et al 1981; Pilc & Vetulani 1982a,b). Each sample contained 450 μl of membrane suspension (P_2 fraction, ca. 0·7 mg protein), 50 μl of radioligand of final concentration as given in the Table, and 50 μl of displacing agent (clonidine or LSD) in final concn 10 μM. The incubation procedure was the same as used previously.

and clinical schedules of drug application: most early experimental results were obtained after a single administration of the antidepressant agent, and are presently regarded as irrelevant for the explanation of the mode of action of antidepressant treatments (Sulser et al 1978). A discrepancy may be observed also in the case of experimental and clinical application of ECT, as the treatment is much more frequent in animal studies. If ECT is studied as an antidepressant treatment, less rigorous schedules of its application should be investigated. Such studies are also warranted by the findings of Chiodo & Antelman (1980) that even a single electroshock may produce a long-lasting effect that is not changed by subsequent treatment.

The present findings confirm our previous results about the action of ECT on systems associated with α_2 adrenergic and $5HT_2$ receptors (Lebrecht & Nowak 1980; Pilc & Vetulani 1982b; Vetulani et al 1981), and also indicate that these effects may be relevant for the clinical action of ECT because they appear almost similarly expressed after less rigorous schedules, similar to these used in treatment of depression (Kiloh 1977). Moreover, they suggest a parallelism between the behavioural effects of ECT and their influence on α_2 and $5\text{-}HT_2$ receptors: the changes in radioligand binding were observed in groups in which behavioural responses were altered.

The present results show also that if the number of shocks is too small or if they are spaced too far apart, the effect of ECT on noradrenergic and 5-hydroxytryptaminergic systems disappears. Thus, in contrast to the effect on dopamine autoreceptors (Chiodo & Antelman 1980), the changes brought about by ECT in the systems investigated in the present study are dependent on repeated treatment.

The present results, and also those suggesting that the upregulation of α_1-adrenoceptors by antidepressants (Vetulani & Pilc 1982) is also produced by spaced ECT (to be published), indicate that an application of ECT less frequent than daily may be a useful experimental approach in the studies of ECT as a model antidepressant treatment. Apparently, four or five electroshocks given at 72 h intervals seem to be the most suitable procedure using the rat as model. The advantages include greater convenience of experimental protocol and the need for fewer experimental animals.

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LY141865, a D_2-dopamine agonist, increases acetylcholine concentration in rat corpus striatum

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Stimulation of dopamine receptors leads to a decrease of acetylcholine (ACh) release (Stadler et al 1973) and turnover (Trabucchi et al 1975; Guyenet et al 1975) and an increase of ACh concentrations in the corpus striatum (McGeer et al 1974). D_2-dopamine (DA) receptors are believed to mediate the tonic inhibitory influence on intrinsic cholinergic neurons in the striatum (Sethy 1979; Euvrard et al 1979; Scatton 1982).

Recent studies have identified a partial ergoline, LY141865, as a D_2-specific DA agonist which stimulates DA receptors without an activation of adenylate cyclase (Tsuruta et al 1981). In agreement with earlier conclusions (Sethy 1979; Euvrard et al 1979; Scatton 1982), we found in the present studies that administration of the D_2 agonist, LY141865, caused an increase of striatal ACh concentrations. In addition, the ergoline DA agonist, pergolide, which activates the striatal adenylate cyclase (Wong & Reid 1980; Goldstein et al 1980), had a similar pharmacological profile of a dopamine agonist as LY141865, but was more potent (Fuller et al 1979; Rabey et al 1981). Pergolide also increased ACh concentrations in striatum. On the other hand, 3-PPP, a putative agonist for the autoreceptors of dopamine (Hjorth et al 1981), did not affect striatal ACh.

Method

Male Sprague-Dawley rats, 100–150 g, were obtained from Harlan Industries, Cumberland, IN, and fed Purina Chow freely for at least three days in a 24 °C room. Pergolide mesylate (8β-[(methylthio)methyl]-6-propylergoline monomethanesulfonate), LY141865 (*trans*-(±)-4a,5,6,7,8,8α,9-octahydro-5-propyl-2H-pyrazole[3,4,-g]quinoline dihydrochloride) and 3-PPP (3-[3-hydroxyphenyl]-*N*-n-propylpiperidine) were injected i.p. and the rats decapitated 30 min later. Striata were rapidly dissected and placed on dry ice before analysis. ACh concentration was determined by radiochemical procedures (Shea & Aprison 1973; Smith et al 1975).

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Results

Table 1 shows the effects of 0·1, 0·3 and 0·6 mg kg^{-1} i.p. doses of LY141865 on ACh concentrations in corpus striatum. These were significantly increased, 29 and 44% respectively, with the two higher doses of LY141865 within 30 min of administration. An average ED50 (dose producing half-maximal response) of 0·5 ± 0·1 mg kg^{-1} i.p. was obtained from three separate determinations. A statistically significant increase of 52% in ACh was also found with the highest dose (0·3 mg kg^{-1} i.p.) of pergolide, and the increase with the two lower doses of pergolide was relatively small (10%). An average ED50 of 0·25 mg kg^{-1} i.p. was estimated for pergolide from two separate determinations. No significant effect of 3-PPP in doses of 10, 30 and 50 mg kg^{-1} i.p. was found in striatal ACh concentrations, while the administration of haloperidol at 5 mg kg^{-1} i.p. brought a 36% decrease. DA-antagonists are known to lower ACh levels (McGeer et al 1974).

Discussion

These data show that LY141865 elevates striatal ACh concentrations, an indication of a decrease of ACh utilization and turnover (Guyenet et al 1975; Trabucchi et al 1975). Two other ergoline dopamine agonists, lergotrile and bromocriptine, also produced increases of ACh levels at relatively high doses of 3 and 10 mg kg^{-1} i.p., respectively (Sethy 1979). These three drugs (LY141865, lergotrile and bromocriptine) have been classified as D_2 agonists since they failed to activate the striatal adenylate cyclase in-vitro (Tsuruta et al 1981; Kebabian & Calne 1979). Therefore, it is consistent with the idea that D_2 receptors are responsible for exerting the inhibitory influence on intrinsic cholinergic neurons in striatum (Sethy 1979; Euvrard et al 1979).