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DOPAMINE POSTSYNAPTIC RECEPTOR EFFECTS OF RESTRICTED SCHEDULES OF ELECTROCONVULSIVE SHOCK

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SUMMARY

Little work is available on the acute and time-dependant dopaminergic effects of single electroconvulsive shock (ECS) and multiple ECS despite the posited clinical utility of such schedules of electroconvulsive therapy (ECT) administration and the posited role of dopaminergic mechanisms in neuropsychiatric disorders. In this study, using the apomorphine-induced motility-alteration behavioural paradigm, single session multiple ECS was found to produce no significant effect while single ECS behaviourally downregulated dopamine postsynaptic receptor functioning one week after the ECS, which effect was also seen (albeit to a lesser extent) a further week later. These findings indicate a possible application of restricted schedules of ECT to dopamine postsynaptic receptor supersensitivity syndromes. Lines for future research are suggested.

Historically and heuristically, the dopaminergic neurotransmitter system is considered to play a key role in the mechanisms underlying various neuropsychiatric disorders. Studies on the dopaminergic effects of electroconvulsive shock (ECS) have largely focused on serial (administered daily or on alternate days as a 'course') schedules of administration (Gleiter and Nutt, 1989); single ECS studies have predominantly addressed dopamine (DA) autoreceptor effets (e.g. Chiodo and Antelman, 1980; Gangadhar et al., 1990), while only one study has evaluated DA postsynaptic receptor changes (Wielosz, 1983); DA effects of multiple ECS (where 2 or more convulsions are induced per session) have not been studied at all.

Since both single and multiple ECT have potentially important clinical applications (Andrade, 1990), the present study sought to assess the acute and time-dependant effects of single ECS and single sesssion multiple ECS on DA postsynaptic receptors in the rat brain.

Material and Methods

DA postsynaptic receptor functioning was studied using the apomorphine-induced motility-alteration behavioural paradigm (Srinivasan et al., 1989).

Adult, male Sprague-Dawley rats (220-240 gms), housed two per cage with free access to tap water and standard laboratory diet, were brougth into a temperature and humidity controlled, 12 hour light-dark cycle (lights on at 6 a.m.), sound-proof, insulated room one week prior to starting the experiment, and were maintained in this environment until the end of study.

In each pair, one rat received true ECS and the other, sham ECS. In the single ECS experiment, just one ECS was administered; in the multiple ECS experiment, three ECS were administered, one after the other, with an interval of 3 minutes in between this gap was to ensure that no ECS was administered during the refractory period occasioned by the previous ECS (after Maleizky, 1987).

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ECS were administered between 9 and 10 a.m. to unanaesthetized rats in a specially designed perspex glass cage which was oxygenated during the treatment. An ECT stimulus generator, designed and constructed by the research team (Gangadhar et. al, 1988), was used to deliver 90 volts of 50 Hz alternating (unmodified) sinusoidal wave current for 0.5 secs. through saline soaked earclip electrodes; voltage and current stimulus parameters were noted from a digital display unit, while (motor) seizure duration elicited was timed using a stopwatch. Sham ECS involved an identical procedure except that no electrical stimulus was delivered.

Between 9 a.m. and 1 p.m. on days 1, 8 and 15 after true and sham ECS, the rats (one pair at a time) were monitored on motility parameters of DA post-synaptic receptor function. The rats were subcutaneously (nape of the neck) injected with either normal saline (1ml/kg) or freshly-dissolved (2mg/kg) apomorphine (SIGMA Chemicals) in a volume of 1ml/kg. Following the injection, the rats-one true ECS-treated and one sham ECS-treated at a time were placed in separate Opto-Varimex monitoring cages (Columbus Instruments). Each cage measures 42 cm × 42 cm and contains infra-red emitters and sensors, 15 of each located on the x and on the y axes of the cage. Interruptions of the infra-red beams are sampled at the rate of 4 per second in an interfaced Apple II Plus computer using the Autotrack Programme. The data herein generated describe 8 parameters of motility distance travelled (by the rat, during the period of monitoring), time spent resting, time spent ambulating, time spent engaged in stereotypic behaviour, number of bursts of stereotypic movements. and number of vertical, clockwise and anticlockwise movements.

Motility was monitored in the 2 cages simultaneously for a period of 21.25 minutes, commencing 5 minutes after the injection; this time interval allowed for adaptation of the rat to the experience of being handled and placed in a new situation, as well as for onset of drug action after absorption. The monitoring cages were kept in the same insulated, disturbance-free environment so that all potential stimuli (including sound, light, temperature and humidity) were controlled and kept constant all through the monitoring.

A few methodological notes are relevant here for the benefit of clinicians who have had no exposure to basic science research procedure. Baseline (pre-ECS) motility recordings were considered unnecessary as all rats were of the same age, sex, body weight and in-bred strain; the baseline motility scores would hence be closely similar.

The experimental and control groups were ECS + apomophine and sham ECS + apomorphine treated rats respectively. In order to eliminate discrepancies in motility occasioned by ECS-induced perturbations in non-dopaminergic neurotransmitter and neuromodulater systems, ECS and sham ECS treated internal control groups were used, injected with saline in place of apomorphine. Thus, the experimental set-up was a (2 × 2) factorial design.

Statistical analysis involved the use of a 2 × 2 Two Way ANOVA after logarithmic transformation of data to homogenize the variances. Since the null hypothesis was that the ECS + apomorphine and sham ECS + apomorphine groups did not differ, only the ECS × apomorphine interaction (and not the main effects for ECS vs sham ECS, and apomorphine vs saline) was relevant to the objectives of the study.

Results

Despite fluctuations at the electricity mains, the delivered voltage was kept relatively constant during the ECS, ranging between 90 and 92 volts. Wide variation was however noted in the amperage of the current delivered; currents in the range of

10-40 mA were recorded. Such is however not unusual as impedance between the electrodes is known to vary extensively between subjects (in both human and animal populations) and across time. All motor seizures elicited were between 15 and 25 seconds in duration. By conventional standards, therefore, all rats experienced adequate (tonic-clonic) convulsions.

As internal correlations between the various parameters of motility were high, and as distance travelled by the rat during the period of monitoring was the most sensitive index of drug induced change in motor behaviour, only the data related to this motility parameter are presented (Tables 1 and 2). From Table 3 it is apparent that there was a significant difference between the experimental and control groups (ECS × apomorphine interaction) only at day 8 in the single ECS experiment, which effect was near significantly seen a further week later; the experimental and control groups did not differ in the single session multiple ECS experiment on any of the days of assessment.

The single significant interaction noted above was in the direction of greater responsiveness of sham ECS-treated animals to apomorphine as compared with the ECS-treated animals; furthermore, while the responsiveness to apomorphine did not change in the single ECS group between day 1 and 8 (paired t test), it significantly increased in the sham ECS group (paired $t = 2.60$, d.f. $= 7$, $p < 0.05$).

Discussion

Neither single ECS nor single-session multiple ECS exerted acute DA postsynaptic receptor effects, as evidenced by an absence of a significant interaction effect at Day 1 in either experiment.

At day 8 in the single ECS experiment, an interesting finding emerged: the expected DA postsynaptic receptor sensitization (Andrade and Pradhan, 1990; Andrade et al., 1990), induced by the administration of apomorphine during the day 1 assessments, was observed in the sham ECS-apomorphine but not in the true ECS-apomorphine group. this difference was significant, as evidenced by the statistically significant interaction effect. At day 15, the same finding just failed to reach statistical significance, suggesting that the ECS effect develops in the first week and wanes during the next.

The failure of single ECS-treated animals to develop DA postsynaptic receptor supersensitivity may either be because single ECS produces behavioural DA postsynaptic receptor down-regulation (an observation supported by Wielosz, 1983) or because single ECS inhibits the process whereby DA postsynaptic receptors become supersensitive. The former possibility suggests the utility of restricted schedules of ECT in the treatment of putative DA postsynaptic receptor supersensitivity syndromes (e.g. tardive dyskinesia,), while the latter possibility suggests the use of such schedules of ECT in the prophylaxis of such syndromes.

Serial ECT is known to upregulate DA postsynaptic receptors (Gangadhar et al., 1989), a change directly opposite to the first possibility suggested above. Hence, it is speculated that the paradoxical ability of ECT to either benefit or worsen tardive dyskinesia (Sackeim and Mukherjee, 1989) may depend on whether the course of ECT administered is functionally either 'restricted' or 'serial'.

The second possibility suggested above has a curious parallel: Lerer et al. (1982) found that spaced serial ECS prevented the development of haloperidol-induced DA postsynaptic receptor supersensitivity in rats.

Both of these suggested possibilities can be empirically tested in suitably designed experiments.

Table 1 : Single ECS experiment : Mean ± SEM distance travelled (in cm.) by apomorphine and saline-injected, ECS-and sham ECS-treated rats monitored 1, 8 and 15 days after ECS.

	ECS-apomorphine group (n=8)	ECS-saline group (n=8)	Sham ECS-apomorphine group (n=8)	Sham ECS-saline group (n=8)
Day 1	2365.6±244.5	1388.3±198.6	2093.3± 368.6	1295.1±287.2
Day 8	2604.3±450.8	1239.5±264.1	5792.0±1518.8	977.1±184.9
Day 15	3551.9±893.8	1272.4±301.1	6689.6±1351.6	1064.0±211.4

Table 2 : Multiple ECS experiment : Mean ± SEM distance travelled (in cm.) by apomorphine-and saline-injected, ECS-and sham ECS-treated rats monitored 1, 8 and 15 days after ECS.

	ECS-apomorphine group (n=9)	ECS saline group (n=9)	Sham ECS-apomorphine group (n=9)	Sham ECS-saline group (n=9)
Day 1	3172.6± 513.7	1374.2±186.6	3852.7± 899.6	2114.0±247.6
Day 8	5170.0± 939.5	1715.8±200.3	5928.6±1429.7	1299.3±192.1
Day 15	6824.4±1244.9	2427.3±338.2	8015.2±1318.5	1745.3±138.4

Table3: Two way ANOVA F values in the single (d.f. 1, 28) and multiple (d.f. 1, 32) ECS experiments.

	Single ECS experiment			Multiple ECS experiment		
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15
Main effect: ECS vs sham ECS	0.86	1.08	1.15	8.94***	0.89	0.05
Main effect: apomorphine vs saline	11.78***	34.31***	23.45***	26.98***	35.21***	51.59***
Interaction effect: ECS X apomorphine	0.05	4.44***	2.98	0.07	0.19	2.17

*p<0.10, **p<0.05, ***p<0.01

The failure of multiple ECS to produce significant change could be because multiple ECS, wherein convulsions are repeatedly elicited is physiologically entirely different from single or serial ECS, and hence need not necessarily induce comparable effects to these 2 schedules of ECS administration.

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