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Chronic electroconvulsive shock alters hypothermic response of B-HT 920 and SKF 38393 in rats

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Abstract—The hypothermic response of B-HT 920, a D_2-dopamine agonist remained unaltered while that of apomorphine, a mixed D_1-/D_2-agonist was significantly reduced following chronic electroconvulsive shock (ECS) treatment. SKF 38393 (5 mg kg^{-1}), a selective D_1-agonist potentiated the hypothermic response of B-HT 920 in non-ECS-treated rats. The response of the combination was, however, attenuated following chronic ECS treatment. These observations suggested a reduction in D_1-receptor density following chronic ECS treatment in rats.

Chronic electroconvulsive shock (ECS) treatment has been reported to enhance the behavioural response induced by D_1- but not D_2-dopamine agonists (Kingston et al 1988). Contrary to this observation, a decrease in the density of D_1-receptors in rat brain has been reported to occur following repeated treatment with ECS (Klimek & Nielsen 1987; Maj et al 1987). With this background the present study was undertaken to assess the efficacy of the selective D_1-agonist SKF 38393 (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol) (Setler et al 1978) for D_1-receptors following chronic ECS treatment. Since the D_1-receptor system has been reported to modulate the D_2-receptor system (Pifl & Hornykiewicz 1988; Verma & Kulkarni 1991a, b), the effect of SKF 38393 on the hypothermic response of B-HT 920 (2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo- (4,5-d)-azepine), a postsynaptic D_2-agonist (Hjorth & Carlsson 1987) was studied in rats chronically exposed to ECS.

Materials and methods

Wistar rats of either sex, 150–200 g (bred in the Central Animal House facility of Panjab University, Chandigarh) had free access to food and water and were housed under standard laboratory conditions. ECS (current 150 mA, 0·2 s) was given through corneal electrodes. The rats received either a single (acute treatment) or a series of 10 shocks at 24 h intervals (chronic treatment). In sham rats the ear clip electrodes were connected but no current was applied. Animals were tested 24 h after either acute or chronic ECS treatment. The experimental protocol was approved by the departmental research committee.

Measurement of rectal temperature. The variation in rectal temperature was recorded using telethermometry (Yellow Springs Instrument Co., Inc., USA) by inserting the thermistor probe to a depth of 2–3 cm into the rectum. Rectal temperature of each animal was recorded before drug administration and 15, 30, 60, 90 and 120 min after drug administration. The temperature of each animal was recorded for a period of 1 min. All the experiments were performed between 0900 and 1200 h. There was no significant variation in the rectal temperature of control animals during this period.

Drugs. Drug solutions were made in distilled water and administered intraperitoneally in a constant volume of 0·5 mL/100 g of body weight, either alone or in combination. The antagonists were administered 30 min before the agonists. Each group comprised 5 to 10 animals. The drugs used were: B-HT 920 (Boehringer Ingelheim, Germany), apomorphine (Sigma, USA), SKF 38393 (Research Biochemicals Inc., MA, USA) and SCH 23390 (7-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol; Schering Plough Co., Bloomfield, NJ, USA).

Statistical analysis. The data are expressed as mean (°C ± s.e.m.) change in rectal temperature. The results were analysed by one-way analysis of variance with 95% confidence ($P < 0.05$ being significant), and also compared using Student's *t*-test.

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Results

Effect of ECS treatment on B-HT 920-induced hypothermia. Acute ECS treatment did not produce any significant alteration in the hypothermic response of B-HT 920 (0·5 mg kg^{-1}) when compared with non-ECS-treated rats. Similarly, after chronic ECS treatment B-HT 920 (0·5 and 1·0 mg kg^{-1}) produced the same degree of hypothermia as in non-ECS-treated controls (Table 1).

Effect of ECS treatment on apomorphine-induced hypothermia. Chronic ECS treatment produced a significant reduction in the hypothermic response of apomorphine (0·5 mg kg^{-1}) in comparison with the corresponding non-ECS-treated control (Table 1).

Modification of the response of B-HT 920 by SKF 38393 in non-ECS- and chronically ECS-treated rats. In non-ECS-treated rats SKF 38393 (5 mg kg^{-1}) potentiated the hypothermic response of B-HT 920 (0·5 mg kg^{-1}). The response of the combination was blocked by SCH 23390 (1 mg kg^{-1}). Following chronic treatment with ECS, the combination of B-HT 920 (0·5 mg kg^{-1}) plus SKF 38393 (5 mg kg^{-1}) produced the same degree of fall in rectal temperature as B-HT 920 (0·5 mg kg^{-1}) alone. The response due to the combination was lower than that in non-ECS-treated rats. A higher dose of SKF 38393 (10 mg kg^{-1}) was, however, required to potentiate the response of B-HT 920 in chronic ECS-treated rats (Table 1).

Discussion

ECS produces many neurochemical alterations in the dopaminergic system which may be related to its efficacy in the treatment of Parkinson's disease (Andersen et al 1987). Repeated ECS therapy has been shown to increase dopamine-mediated behaviour in rodents. Corresponding alterations in dopamine receptor binding, however, remain to be demonstrated (Green & Nutt 1987). ECS-induced potentiation of locomotor and stereotyped behaviour and of apomorphine-induced rotation in unilaterally 6-hydroxydopamine-treated rats pointed to the likely increase in the number of D_1-receptors (Fochtmann 1988). Subsequently, ECS was shown to specifi-

Table 1. Modification of thermogenic action of various dopamine agonists following electroconvulsive shock treatment (ECS).

Group	Treatment	Dose (mg kg^{-1})	n	ECS	Mean fall in rectal temperature (°C ± s.e.m.)
1	Saline	—	5	—	0·38 ± 0·14
2	B-HT 920	0·5	8	—	2·44 ± 0·21*
3	B-HT 920	1·0	7	—	3·62 ± 0·23*
4	Apomorphine	0·5	6	—	2·75 ± 0·22
5	B-HT 920	0·5	6	—	4·33 ± 0·21*
	+ SKF 38393	5·0			
6	SCH 23390	1·0	5	—	1·33 ± 0·23*
	+ B-HT 920	0·5			
	+ SKF 38393	5·0			
7	B-HT 920	0·5	6	Acute	2·6 ± 0·15
8	B-HT 920	0·5	7	Chronic	2·7 ± 0·18
9	B-HT 920	1·0	10	Chronic	3·7 ± 0·25
10	Apomorphine	0·5	7	Chronic	1·0 ± 0·24*
11	B-HT 920	0·5	8	Chronic	3·0 ± 0·32*
	+ SKF 38393	5·0			
12	B-HT 920	0·5	7	Chronic	5·0 ± 0·14*
	+ SKF 38393	10·0			

The maximum fall in body temperature observed at peak time is expressed as mean (°C ± s.e.m.) fall in rectal temperature, mean control rectal temperature being 38.6 ± 0.15°C. * $P < 0.05$ compared with respective control groups as analysed by Student's t-test and one-way analysis of variance. F-ratio (10, 63) = 22·86, $P < 0.05$.

cally enhance behavioural responses induced by D_1- but not D_2-agonist treatment (Kingston et al 1988). Other studies demonstrated that repeated treatment with ECS decreases the density of D_1-receptors in the rat brain (Klimek & Nielsen 1987; Maj et al 1987).

Our experiments demonstrate that acute or chronic ECS treatment does not alter the hypothermic response of B-HT 920. This suggests that treatment with ECS does not alter D_2-agonist-induced behavioural responses (Kingston et al 1988). The potentiation of the hypothermic action of B-HT 920 by SKF 38393 was sensitive to blockade by the D_1-antagonist, SCH 23390 (Iorio et al 1983) suggesting a facilitatory effect of D_1-stimulation on the D_2-receptor-mediated hypothermic response of B-HT 920. Insufficient D_1-receptor stimulation might explain the inability of SKF 38393 to potentiate the hypothermic action of B-HT 920 following chronic ECS treatment. Similarly, the reduced hypothermic response of apomorphine, a mixed D_1-/D_2 agonist, after ECS parallels the result obtained with B-HT 920 plus SKF 38393 (5 mg kg^{-1}) further suggesting reduced D_1-receptor stimulation. Our findings are consistent with the predictions of alterations in D_1-receptors with ECS as reported by Klimek & Nielsen (1987). The observation that the response of B-HT 920 (0·5 mg kg^{-1}) is potentiated after increasing the dose of SKF 38393 (10 mg kg^{-1}) is also consistent with a decrease in the effectiveness of SKF 38393 because of down-regulation of D_1-receptor stimulation.

The present study, therefore, indicates that chronic ECS treatment reduced D_1-receptor-mediated behavioural responses probably by downregulating D_1-receptors. Since D_1-receptor activation is known to modify the D_2-receptor mediated response, the observed reduced hypothermic response could be due to the alterations in the density of D_1-receptors following chronic ECS treatment. This may have implications in the clinical efficacy of ECS in treating psychotic symptoms in depression as well as Parkinson's disease.

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