

INFLUENCE OF DOPAMINERGIC RECEPTOR SUPERSENSITIVITY ON ANTICONVULSANT ACTION OF CARBAMAZEPINE

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Summary : Dopamine (DA) receptor supersensitivity was induced in albino rats by haloperidol (5 mg/kg, ip day, for 18 days) and after 48 hr carbamazepine (CBZ) was administered in graded doses. The animals were subjected to Maximal Electroshock Seizures (MES) test, Minimal Electroconvulsive Threshold (MET) test and Pentylentetrazole (PTZ)-induced convulsions test. Haloperidol pretreatment marginally increased the effect of CBZ against PTZ induced seizures, but not against electrically induced seizures (MES and MET tests).

Key words : dopamine receptor supersensitivity

seizures

haloperidol

carbamazepine

pentylentetrazole

INTRODUCTION

Despite the accumulating evidence of a variety of neurotransmitters, neuromodulators and neurohumoral systems that are affected by carbamazepine (CBZ) not much is known about the mechanisms of its anticonvulsant action. Earlier a preferential role of noradrenaline (NA) in modulating its anticonvulsant action was suggested (7, 8). Cerebral and spinal cord 5-HT neurons did not play a crucial role in mediating the anticonvulsant action of CBZ (2). Recently it has been found that adenosine system has no role in the anticonvulsant effects of CBZ on amygdaloid kindling (1, 9). Whole brain GABA levels in mice are also not changed by CBZ (6). Gee *et al.* (4) have provided evidence for the possible involvement of altered DA receptors in amygdaloid kindlings in rats. DA receptor supersensitivity is a necessary prerequisite for increased seizure resistance in the evolution of kindling. This data suggests an important role for DA in kindled seizure suppression. The study examines the effect of prior haloperidol induced DA receptor supersensitivity ("up regulation") on the anticonvulsant

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activity of CBZ and aims to establish the relationship, if any, of CBZ and the dopaminergic system.

MATERIAL AND METHODS

Albino rats (150 g) of either sex were employed. Dopaminergic (DA) receptor supersensitivity was produced by administration of haloperidol, 5 mg/kg/day, ip for 18 days (4). The anticonvulsant effect of CBZ was studied once before and after haloperidol treatment using suitable tests, viz., maximum electroshock seizures (MES); minimum electro convulsive threshold (MET) and pentylenetetrazole (PTZ) induced convulsions.

MES was induced with AC (150 mA) given for 0.2 sec through ear clip electrodes. Only those animals showing the hind limb tonic extensor phase (HLE) in prior tests were selected for subsequent work. The following day control and test animals ($n=6$) were given CBZ in graded doses of 2.5, 5, 10 and 20 mg/kg, ip and 45 min later they were re-tested for MES. The next day test animals were started on haloperidol 5 mg/kg, ip for 18 days, while controls were given vehicle of haloperidol. CBZ testing commenced 48 hr after the last dose of haloperidol. CBZ was readministered and MES test performed 45 min later. 't' test was used in analysis of final data using % protection due to CBZ.

The MET's were determined using 0.2 sec electroshock of increasing intensity starting from 0.5 mA with increments of 1 mA. The appearance of neck jerk was taken as the end point. On day 1, baseline thresholds were determined for all animals, shock being given at intervals of 30 mins. MET's were ascertained 45 mins after CBZ (10 mg/kg, ip) in test and control animals ($n=6$ each) before and 48 hr after chronic treatment with haloperidol. The median threshold was determined for each group and the significance of the difference tested by student's 't' test.

Clonic convulsions were induced by PTZ (60 mg/kg, sc, a dose predetermined to produce typical convulsions in 100% animals). Doses of CBZ (2.5, 5, 10, 15 and 20 mg/kg, ip) were administered to control and test groups ($n=6$ per group) which were pretreated with vehicle or haloperidol respectively. 45 min following CBZ, PTZ was administered. Absence of myoclonic jerks or convulsions during a 20 min period after PTZ was considered as the parameter for anticonvulsant activity. The percentage of animals protected by various doses of CBZ in control and test group were compared and differences determined.

Drug used were : Haloperidol BP (5 mg/ml solution, Seranace-Searle (India) Ltd., diluted with normal saline and Carbamazepine (M/s. S. G. Pharmaceuticals).

For the electroshock tests, CBZ was dissolved as reported earlier (5). For chemoshock tests CBZ was dissolved in 50% propylene glycol, 20% Ethanol and 30% water with slight warming on a water bath and was administered in the volume of 1 ml/kg, ip.

RESULTS

Effect of CBZ on prior Haloperidol induced supersensitivity following :

MES: The initial marked haloperidol induced catatonia, immobility and sedation gradually decreased and the rats were almost normal towards end of treatment. 45 min following administration of CBZ (2.5, 5 and 10 mg/kg, ip) the protection was $60 \pm 15.5\%$, $80 \pm 12.7\%$ and 100% respectively. Similar protective values were obtained in controls. Chronic haloperidol treatment *per se* did not have any anticonvulsant effect nor did it modify the anticonvulsant potency of CBZ at any of the doses examined.

MET: The effect of CBZ (10 mg/kg) *per se* with respect to baseline on convulsive thresholds in the MET test in haloperidol pretreated groups is shown in Table I (columns 1 vs 3). CBZ, significantly raised the MET threshold from 6.0 ± 0.21 mA to 15.5 ± 0.5 mA. However, the increase in threshold produced by CBZ in haloperidol pretreated groups 15.5 ± 0.5 mA, was not significantly different from that of its own control group, 17.0 ± 0.63 mA (columns 3 Vs 4)

TABLE I : Effect of CBZ, 10 mg/kg, i.p., on minimal electroconvulsive threshold (in milliamperes) (MET) before and after haloperidol pretreatment for 18 days.

(1)	(2)	(3)	(4)
Baseline threshold (n=18)	Control vehicle of CBZ after haloperidol (n=6)	CBZ after haloperidol (n=6)	CBZ after vehicle of haloperidol (n=6)
6 ± 0.21	6 ± 0.25	$15.5 \pm 0.5^*$	17.0 ± 0.63

* $P < 0.001$ as compared to baseline threshold but (3) and (4) are not significantly different from each other.

PTZ: CBZ (5, 10 and 15 mg/kg) showed 17, 67 and 84% protection, respectively, against PTZ induced seizures in haloperidol pretreated rats. 100% protection was afforded by 20 mg/kg. There was only a marginal (non-significant) increase in terms of % protection and number of myoclonic jerks as compared to saline treated controls.

DISCUSSION

The results show that haloperidol induced DA receptor supersensitivity did not modify the anticonvulsant effect of CBZ in MES or MET tests. CBZ demonstrated anti-PTZ activity, though the increased effect was only marginally better.

Gee *et al.* (4) showed that the rate of kindled seizure development was slowed after haloperidol induced DA supersensitivity suggesting that DA plays a role in seizure suppression. In another study (3) CBZ 100 mg/kg (po) has been shown to inhibit limbic seizures in DA supersensitivity induced by intra-amygdaloid injection of ferric chloride.

In this study the anticonvulsant activity of CBZ was not substantially altered by prior haloperidol induced DA receptor supersensitivity, indicating that dopaminergic systems were not involved in the neuromodulation of CBZ activity. It may therefore be assumed that amygdaloid kindling produced two changes, viz., progressive development of motor seizures and DA receptor sensitivity change (a down regulation) and though haloperidol produces opposite change in DA receptor sensitivity, it does not produce a matching change in thresholds (MET etc.) or carbamazepine action. This probably means that effect of amygdaloid kindling in genesis of generalized seizures is unrelated to DA receptor sensitivity change. This probably explains why no change in upregulation thresholds for seizure (MET) or CBZ effect was produced by haloperidol induced supersensitivity.

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