The Pharma Innovation Journal 2015; 4(8): 136-139

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2015; 4(8): 136-139

www.thepharmajournal.com
Received: 19-06-2015
Accepted: 22-07-2015

Dr. VM Thorat
Department of Pharmacology
KIMS Karad, Maharashtra, India

Dr. Somnth M Matule
Department of Pharmacology
KIMS Karad, Maharashtra, India

Corresponding Author:
Dr. VM Thorat
Department of Pharmacology
KIMS Karad, Maharashtra, India

Investigation of the psychopharmacological profile of carbamazepine

Dr. VM Thorat and Dr. Somnth M Matule

Abstract
Aim: investigate whether CBZ induces the SB by stimulating the postsynaptic striatal D2 and D1 DA receptors either directly or indirectly by releasing DA from the nigrostriatal DA ergic neurons.
Material and Method: Treatment with APO and DAM antagonize the cataleptic effect of HAL, we have therefore investigated whether CBZ treatment reduces the cataleptic effect of HAL.
Result: The effects of CBZ (5 to 20 mg/kg), APO (1.5 and 3 mg/kg) and DAM (5 and 10 mg/kg) treatment on the cataleptic effect of HAL (1 and 1.5 mg/kg) were studied and compared. CBZ at 5, 10 and 20 mg/kg doses was significantly less effective than 1.5 and 3 mg/kg APO and 5 and 10 mg/kg DAM in antagonizing the cataleptic effect of 1 and 1.5 mg/kg HAL. Our results indicate that CBZ, on weight basis, is significantly less effective than APO and DAM in exerting the anticataleptic effect.
Conclusion: CBZ indicate that there is a functional interaction between the corticoglutamatergic neurons and the nigrostriatal DAergic neurons. Further, our results lend support to the reports cited in literature stating that the corticoglutamatergic neurons exert an inhibitory influence on the nigrostriatal DA ergic neurons indirectly by releasing GABA from the intrinsic striatal GAB Aergic interneurons, the striatonigral GABAergic neurons and the GABAergic neurons located in the SNc

Keywords: carbamazepine, psychopharmacological profile.

Introduction
Carbamazepine (CBZ) was initially introduced for the treatment of Trigeminal Neuralgia and is considered to be a primary drug for the treatment of Partial and Generalized Tonic Clonic Seizures. CBZ produces its antiepileptic action by blocking voltage-dependent sodium channels (Na+) and thereby inhibiting the release of glutamate.1 Recently, CBZ is also being used as an antimanic agent in the treatment of Bipolar Affective Disorders [2].
CBZ has a 55-65% clinical response rate in mania, and is as fast acting and effective as Lithium. CBZ is superior in all respects, especially in unipolar depressed patients [3, 4, 5]. CBZ causes rapid clinical improvement in patients with more severe mania and dysphoria, in rapid cyclers with more previous admissions, and in patients without a family history of mania [6, 7].
CBZ, by blocking the voltage-dependent Na+ channels, inhibits the release of glutamate from the corticostriatal and corticonigral glutamatergic neurons and thereby produces a functional lack of glutamate in the striatum and SNc respectively. It was therefore thought worthwhile to investigate the psychopharmacological profile of CBZ pertaining to its effects on the functioning of nigrostriatal DAergic system. The present behavioral study investigating the effects of CBZ pretreatment on behaviors dependent on the functional status of nigrostriatal D Aergic system is undertaken in rats.

Materials and Method
Animals
Albino rats of either sex (weighing 100-180 g), bred in Central Animal House Facility of the Institute, were used. The animals were housed under standard conditions, maintained on a 12 hr light/dark cycle and had free access to food and water up to the time of experimentation. The animals were brought to the department and kept in a noiseless diffusely illuminated laboratory, at least 1 hr before the experiments for acclimatization to the laboratory environment. Each group consisted of 10 animals. Each animal was used only once. All observations were made between 10 and 17 hrs at 27°-30 °C. Observations were made blind with respect to the treatments used.
The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) and conducted according to the Indian National Science Academy (INSA) Guidelines

for the use and care of experimental animals.

Drugs

Drugs used were carbamazepine (Cipla Ltd.), dexamphetamine sulphate (Koch-Light), apomorphine hydrochloride (Sigma), alphamethyl-p-tyrosine methyl ester hydrochloride (Sigma) and haloperidol (Senorm injection, Sun Pharmaceuticals). Carbamazepine (CBZ) was dissolved in (50:50 v/v) dimethylsulfoxide (DMSO) and 0.9 % normal saline. Dexamphetamine (DAM) and alpha-methyl-p-tyrosine (AMT) were dissolved in distilled water while apomorphine (APO) was dissolved in distilled water containing 0.2 mg/ml ascorbic acid. Haloperidol (HAL) injection solution was diluted to required strength with distilled water. All drug solutions were prepared immediately before use and were injected intraperitoneally. The volume of injection was 2 ml/kg body weight for carbamazepine and other remaining drugs. While it was 5 ml/kg body weight for alpha-methyl-p-tyrosine.

Drug doses, routes of administration and the testing time intervals were selected based on previous studies conducted in our laboratory and those reported in literature.

Carbamazepine treatment on the cataleptic effect of haloperidol in rats: For observation and measurement of catalepsy the animals were placed in individual Perspex cages (30×20×20 cm), 30 min before drug treatment to allow adaptation to the new environment. Animals were tested for catalepsy according to the method of Costall and Naylor by placing both front limbs of the animal over an 8 cm high wooden block and measuring the time for which the animal maintained the imposed posture. Scoring, modified from that of Costall and Naylor was as follows: maintaining the imposed posture 0-10 sec (0); 11-30 sec (1); 31-60 sec (2); 61-120 sec (3); 121 sec and more (4).Control groups received HAL (1 and 1.5 mg/kg i.p.) followed 0.5 hr later by vehicle (2 ml/kg i.p. of 50:50 v/v DMSO: normal saline). Experimental groups received HAL (1 and 1.5 mg/kg i.p.) followed 0.5 hr later by CBZ (5, 10 and 20 mg/kg i.p.). Animals were tested for catalepsy 1 hr after vehicle or CBZ injection. Catalepsy score of each animal in the group was taken to compute the mean value of the group.

Haloperidol, alpha-methyl-p-tyrosine and small doses of apomorphine on stereotyped behaviour induced by carbamazepine, high doses of apomorphine and dexamphetamine in rats: For observation of SB, the rats were placed in individual cages made of wire netting, measuring 30×20×20 cm, 30 min before drug treatment to allow adaptation to the new environment. The intensity of SB was assessed over a 30 sec observation period at 10 min intervals throughout its duration, using the scoring system of Costall and Naylor where periodic sniffing = 1, continuous sniffing = 2, periodic biting, gnawing or licking = 3 and continuous biting, gnawing or licking = 4. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group. HAL (0.25 and 0.5 mg/kg i.p.) and small doses of APO (0.05 and 0.1 mg/kg i.p.) were injected 30 and 60 min respectively before CBZ (2.5, 5, 10, and 20 mg/kg i.p.), APO (1.5 and 3 mg/kg i.p.) or DAM (5 and 10 mg/kg i.p.) Control groups received vehicle (50:50 v/v DMSO: 0.9% normal saline i.p.) 30 min before receiving CBZ, APO or DAM. AMT (100 and 200 mg/kg i.p.) was injected 4 hr prior to CBZ (2.5, 5, 10 and 20 mg/kg i.p.), APO (1.5 and 3 mg/kg i.p.) or DAM (5 and 10 mg/kg i.p.). Control groups received (5 ml/kg i.p.) 4 hr before receiving CBZ, APO or DAM.

High dose Apo morphine treatment on the cataleptic effect of haloperidol in rats: Control groups received HAL (1 and 1.5 mg/kg i.p.) followed 0.5 hr later by distilled water (2 ml/kg i.p.). Experimental groups received HAL (1 and 1.5 mg/kg i.p.) followed 0.5 hr later by APO (1.5 and 3 mg/kg ip). Animals were tested and scored for catalepsy 20 min after distilled water or APO injection in the same manner as described under the heading 'Carbamazepine treatment on the cataleptic effect of haloperidol in rats'. Catalepsy score of each animal in the group was taken to compute the mean value of the group**.**

Dexamphetamine treatment on the cataleptic effect of haloperidol in rats: Control groups received HAL (1 and 1.5 mg/kg i.p.) followed 0.5 hr later by distilled water (2 ml/kg i.p.). Experimental groups received HAL (1 and 1.5 mg/kg i.p.) followed 0.5 hr later by DAM (5 and 10 mg/kg i.p.). Animals were tested and scored for catalepsy 1 hr after distilled water or DAM injection in the same manner as described under the heading 'Carbamazepine treatment on the cataleptic effect of haloperidol in rats'. Catalepsy score of each animal in the group was taken to compute the mean value of the group.

Statistics: The results were statistically analysed by the Student's unpaired t-test with differences considered significant at $P<0.05$.

Result

Before embarking on our studies with CBZ we had investigated the effects of vehicle (50:50 v/v DMSO: 0.9% normal saline i.p.) on the gross behaviour of the animals, on the behaviours induced by the DA agonists and on catalepsy induced by HAL. Its effects were compared with control groups receiving distilled water (2 ml/kg i.p.). DMSO did not produce motor incoordination, ataxia or muscular hypotonia; neither did it stimulate locomotor activity or induced stereotyped behaviour or catalepsy in rats. It did not significantly influence the behaviours induced by the DA agonists. Further, DMSO had no significant effect on HAL induced catalepsy. HAL (0.25 and 0.5 mg/kg) did not induce SB in rats in any of the studies wherein it was used. CBZ (5 to 20 mg/kg) induced dosedependent SB in rats. Pretreatment with 0.25 mg/kg HAL abolished the SB induced by 5 mg/kg CBZ and significantly antagonized the SB induced by 10 and 20 mg/kg CBZ. Pretreatment with 0.5 mg/kg ALabolished the SB induced by 5, 10 and 20 mg/kg CBZ.

Alpha-methyl-p-tyrosine 100 and 200 mg/kg did not induce SB or catalepsy in rats in any of the studies it was used. CBZ (5 to 20 mg/kg) induced dose-dependent SB in rats. Pretreatment with 100 mg/kg alpha-methyl-p-tyrosine significantly antagonized the SB induced by 5, 10 and 20 mg/kg CBZ. Pretreatment with 200 mg/kg alpha-methyl-ptyrosine abolished the SB induced by 5 and 10 mg/kg CBZ and significantly antagonized SB induced by 20 mg/kg CBZ. Table 1 shows Effect of pretreatment with small doses of APO on CBZ induced SB in rats. Treatment with 5, 10 and 20 mg/kg CBZ significantly reduced the cataleptic effect of 1 and 1.5 mg/kg HAL. Treatment with 1.5 mg/kg APO abolished the cataleptic effect of 1 mg/kg HAL and

significantly reduced the cataleptic effect of 1.5 mg/kg HAL. Treatment with 3 mg/kg APO abolished the cataleptic effect of 1.5 mg/kg HAL. Treatment with 5 mg/kg DAM abolished the cataleptic effect of 1 mg/kg HAL and significantly reduced the cataleptic effect of 1.5 mg/kg HAL. Treatment with 10 mg/kg DAM abolished the cataleptic effect of 1.5 mg/kg HAL. Treatment with 5, 10 and 20 mg/kg CBZ was significantly less effective than 1.5 and 3 mg/kg APO and 5 and 10 mg/kg DAM inantagonizing the cataleptic effect of 1 and 1.5 mg/kg HAL.

Study 3	Treatment (Dose mg/kg i.p.)	Intensity Score (Mean ± S.E.M.)
A	DW + CBZ 5	1.6 ± 0.16
	APO 0.05 + CBZ 5	0.4 ± 0.16**
	APO 0.1 + CBZ 5	0.0
B	DW + CBZ 10	2.0 ± 0.00
	APO 0.05 + CBZ 10	1.2 ± 0.13*
	APO 0.1 + CBZ 10	0.6 ± 0.16**
C	DW + CBZ 20	2.1 ± 0.13
	APO 0.05 + CBZ 20	1.6 ± 0.16*
	APO 0.1 + CBZ 20	0.5 ± 0.16**

Table 1: Effect of pretreatment with small doses of APO on CBZ induced SB in rats.

Discussion

In the present study, treatment with carbamazepine 5, 10 and 20 mg/kg was found to induce sniffing and OMV type of SB dose dependently within 10-20 minutes lasting for about 30-45 minutes. Further in the present study, pre-treatment with high doses of apomorphine (1.5 and 3 mg/kg i.p.) and of dexamphetamine (5 and 10 mg/kg i.p.) was found to induce SB and OMV of SB in rats. The intensity of SB induced by 5, 10 and 20 mg/kg i.p. carbamazepine was significantly lower than that induced by 1.5 and 3 mg/kg i.p. apomorphine and 5 and 10 mg/kg i.p. dexamphetamine. This indicates that carbamazepine on weight basis, is less potent than apomorphine and dexamphetamine in inducing SB. In the present study, pretreatment with haloperidol antagonized the SB induced by apomorphine and dexamphetamine. This indicates that DAergic mechanisms are involved in the induction of SB by carbamazepine in rats. Carbamazepine might be inducing SB either by, directly stimulating post-synaptic striatal D2 and D1 DA receptors or indirectly by releasing DA from the nigrostriatal DAergic neurons with resultant stimulation of post-synaptic striatal D2 and D1 DA receptors by the released DA.

In the present study, pre-treatment with AMT (100 and 200 mg/kg i.p.) and small doses of APO (0.05 and 0.1 mg/kg i.p.) antagonized the SB induced by CBZ and DAM but did not antagonize the SB induced by high doses (1.5 and 3 mg/kg i.p.) of APO. This indicates that CBZ induces the SB indirectly by releasing DA from the nigrostriatal DAergic neurons and not by direct stimulation of the postsynaptic striatal D2 and D1 DA receptors.

From all the above findings, we have concluded that CBZ does not induce the SB by directly stimulating the postsynaptic striatal D2 and D1 DA receptors but induces the SB by releasing DA from the nigrostriatal DAergic neurons with resultant stimulation of postsynaptic striatal D2 and D1 DA receptors by released DA, concurs with the observation that CBZ acts presynaptically on striatal neurons, mainly through enhancement of DA release and does not displace [3H] spiroperidol binding [7]. Our findings also indicate that CBZ as compared to DAM, is a weak DA releaser. Further, it has been shown that CBZ does not prevent 6-OH DA lesions, suggesting that CBZ has no blocking action upon catecholamine reuptake [8] and it was also shown that CBZ enhances [3H] release *in vitro* from striatal slices while [3H] DA reuptake remains unchanged [7].

Recently, selegeline, a drug which elevates brain DA levels by selectively inhibiting brain MAO-B, was reported to exert antidepressant activity in patients of major depressive disorder (MDD) and to prevent relapse of MDD.Our behavioural study demonstrates that CBZ releases DA from the nigrostriatal DAergic neurons and enhances DA function in corpus striatum. It is possible that CBZ might also be releasing DA from the mesolimbic DAergic neurons and facilitating DA function in the mesolimbic region thereby counteracting depression as suggested by Wang PW [9].

Conclusion

In conclusion, our behavioral study conducted in rats indicates that CBZ does not induce the SB by directly stimulating the postsynaptic striatal D2 and D1 DA receptors. Our study has demonstrated that CBZ induces SB in rats by releasing DA from the nigrostriatal DAergic neurons with resultant stimulation of the post-synaptic striatal D2 and D1 DA receptors by the released DA. Further, our study also demonstrated that CBZ through the released DA, counteracts the cataleptic effect of HAL.

References

1. Baldessarini RJ, Tarazi FI. Pharmacotherapy of Psychoses and Mania. In: Brunton LL, Laso JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11Th ed. New York, McGraw Hill, 2006, 461-500.
2. Ballenger JC. The Use of Anticonvulsants in Manic-depressive Illness.J Clin Psychiatry. 1988; 49:21-25.
3. Okuma T, Yamashita I, Takahashi R, Itoh H, Otsuki S. Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study. Pharmacopsychiatry. 1990; 23:143-50.
4. Stuppaeck C, Barnas C, Miller C, Schwitzer J, Fleischhacker WW. Carbamazepine in the prophylaxis of mood disorders. J Clin Psychopharmacol. 1990; 10:39-42.
5. Liu ZZ, Mei QY, Wan Y. A follow-up study on rapid cycling affective disorders. J West China Uni Med Sciences. 1989; 20:335-7.
6. Post RM, Uhde TW, Roy-Byrne PP, Joffe RT. Correlates of antimanic response to carbamazepine. Psych Res. 1987; 21:71-83.
7. Barros HMT, Braz S, Leitie JR. Effect of Carbamazepine on Dopamine Release and Reuptake in Rat Striatal Slices. Epilepsia. 1986; 27(5):534-7.
8. Quattrone A, Annunziato L, Aguglia U, Preziosi P. Carbamazepine, phenytoin and phenobarbital do not influence brain catecholamine uptake, *in vivo*, in male rats. Arch Int Pharmacodyn Ther. 1981; 252(2):180-5.
9. Wang PW, Ketter TA. Clinical use of CBZ for bipolar disorders. Expert Opin Pharmacother. 2005; 6(16):2887-902.