Indian J Physiol Pharmacol 1996; 40(2): 159-162

EFFECT OF PRE-TREATMENT OF SOME CALCIUM CHANNEL BLOCKERS ON CATALEPSY AND STEREOTYPIC BEHAVIOUR IN RATS

SUCHET D. KHANZODE*, SUNIL M. MAHAKALKAR, N. R. BELORKAR, VISHWAS T. KHARKAR AND MOTIRAM S. MANEKAR

Department of Pharmacology,
Indira Gandhi Government Medical College,
Nagpur - 440 018

(Received on April 15, 1995)

Abstract : Effect of pretreatment of intraperitoneally administered Ca-channel blockers Nifedipine (5, 10, 20 mg/kg). Verapamil (5, 10, 20 mg/kg) and Diltiazem (5, 10, 20 mg/kg) was studied on Haloperidol-induced catalepsy and Methamphetamine-induced stereotypy in albino rats. All these drugs reduced the onset of catalepsy, significantly increased the cataleptic score and delayed the onset and inhibited the Methamphetamine-induced stereotypy. The possible involvement of dopaminergic and adrenergic mechanisms and modification by Ca-channel blockers are discussed.

Key words : catalepsy stereotypy verapamil diltiazem nifedipine

INTRODUCTION

Catalepsy and stereotypy in rats is attributed to changes in dopamine (DA) level at the postsynaptic junction. It is reported that haloperidol-induced catalepsy is due to the block of postsynaptic striatal DA receptor (1) leading to the functional lack of DA at the postsynaptic receptor site. It is also reported that methamphetamine-induced stereotypic behaviour is considered to be due to activation of postsynaptic striatal and mesolimbic dopaminergic receptor by released DA (2, 3). Also stereotypic behaviour in rats is used as a model for testing neuroleptics i.e. for antimaniac and antischizophrenic effects (4). Ca-channel blokers like Verapamil possess DA antagonist property in the brain (5). From the above observation it was thought worthwhile to study the effect of some selective Ca-channel blockers by using parameters like catalepsy and stereotypy; efforts were also made to study the possible mechanisms.

METHODS

Forty Wistar albino rats of either sex, weighing between 150-200 gms, 10-12 weeks of age were housed in four groups having *ad lib* access to food and water. After a week's handling, the three groups were given Nifedipine (5 mg, 10 mg, and 20 mg/kg, ip) respectively and Propylene glycol (PPG) at a dose of 0.1 ml/kg, ip to the control group (6).

In the same manner, Verapamil and Diltiazem were given in the three different doses while control group was given double distilled water (DDW) in same doses. Sixty min after the test drugs Haloperidol (0.5 mg/kg, ip) was given to each group to produce catalepsy. Catalepsy was evaluated by placing the front limbs of the animals over a 8 cm high wooden

*Corresponding Author

block and measuring the time for which the animal maintains the posture. Scoring was done by the modified method of Costall and Naylor (7). Animals were tested for onset and intensity of catalepsy at various time intervals. Catalepsy score of each rat in the group was taken to compute mean value of group.

In another set of experiments, rats were treated with Methamphetamine (7 mg/kg, ip), half an hour after pretreatment with test drugs. Animals were observed for onset and intensity of stereotypic behaviour at different time intervals. Stereotypic behaviour was assessed using a scoring system (7). Maximum intensity of stereotyped behaviour by each rat in a group was taken to compute the mean value of group.

The data are presented as mean ± SEM and tests of significance were made by Student's 't' test.

RESULTS

A. Effect on Haloperidol-induced catalepsy : Nifedipine pretreatment on Haloperidol-induced catalepsy increased the mean cataleptic score at the dose of 10 mg/kg, ip ($P<0.05$) and 20 mg/kg, ip ($P<0.01$) at 30 min and 2 hrs testing time respectively as compared to control (Table I). Verapamil increased the cataleptic score at the dose of 10 mg/kg, ip at 2 hrs and 20 mg/kg, ip at all time intervals (Table II). Similarly, mean cataleptic score was increased by Diltiazem (20 mg/kg, ip) at 20 min (Table III). Nifedipine, Verapamil and Diltiazem also reduced the time of onset of catalepsy at all dose levels.

TABLE I : Effect of pretreatment with Nifedipine on Haloperidol induced catalepsy. Mean cataleptic score is increased at dose of 10 mg/kg, ip and 20 mg/kg, ip at 30 min and 2 hrs testing time significantly, (n=10).

Drug and dose / kg, ip	*Mean onset time (min)*	*Mean cataleptic score ± SEM*		
		30 min	*1 hr*	*2 hr*
PPG (0.1 ml)	17.3	3.1 ± 0.23	3.7 ± 0.15	3.6 ± 0.15
Nifedipine (5 mg)	13.0	3.3 ± 0.26	3.9 ± 0.10	3.7 ± 0.15
Nifedipine (10 mg)	11.8	3.7 ± 0.15*	4.0 ± 00	4.0 ± 00*
Nifedipine (20 mg)	6.0	4.0 ± 00**	4.0 ± 00	4.0 ± 00**

PPG - Propyleneglycol; *P<0.05, **P<0.01

TABLE II : Effect of pretreatment with Verapamil on Haloperidol-induced catalepsy. Mean cataleptic score is increased at dose of 10 mg/kg, ip at 2 hrs and 20 mg/kg, ip at all the time intervals significantly, (n=10).

Drug and dose / kg, ip	*Mean onset time (min)*	*Mean cataleptic score ± SEM*		
		30 min	*1 hr*	*2 hr*
DDW (0.1 ml)	16.7	2.9 ± 0.31	3.7 ± 0.15	3.6 ± 0.13
Verapamil (5 mg)	15.0	3.1 ± 0.18	3.7 ± 0.15	3.9 ± 0.15
Verapamil (10 mg)	12.1	3.1 ± 0.23	3.7 ± 0.15	4.0 ± 00*
Verapamil (20 mg)	8.9	4.0 ± 00*	4.0 ± 00*	4.0 ± 00*

DDW - Double distilled water; *P<0.05

TABLE III : Effect of pretreatment with Diltiazem on Haloperidol-induced catalepsy. Mean cataleptic score is increased at dose of 20 mg/kg, ip at 30 min time interval significantly, (n=10).

Drug and dose / kg, ip	*Mean onset time (min)*	*Mean cataleptic score ± SEM*		
		30 min	*1 hr*	*2 hr*
DDW (0.1 ml)	15.3	3.4 ± 0.22	3.8 ± 0.13	3.8 ± 0.14
Diltiazem (5 mg)	13.0	3.5 ± 0.22	3.8 ± 0.13	3.7 ± 0.16
Diltiazem (10 mg)	10.6	3.8 ± 0.13	4.0 ± 00	4.0 ± 00
Diltiazem (20 mg)	7.0	4.0 ± 00*	4.0 ± 00	4.0 ± 00

DDW - Double distilled water; *P<0.05

B. Effect on Methamphetamine-induced stereotypy : Nifedipine pretreatment significantly reduced the mean stereotypic score in the dose 10 mg/kg, ip at 30 min ($P<0.05$) and 20 mg/kg, ip at all test times significantly ($P<0.01$) except at 4 hrs (Table IV). Verapamil reduced the mean stereotypic score significantly ($P<0.05$, $P<0.01$) at all doses at 15 min and 30 min (Table V). Diltiazem also reduced the mean stereotypic score significantly at 20 mg/kg at all test times ($P<0.05$, $P<0.01$) (Table VI). All these drugs were found to delay the onset of stereotypy.

TABLE IV : Effect of pretreatment with Nifedipine on Methamphetamine-induced stereotypy. There is a significant inhibition of stereotypic score in the dose of 10 mg/kg, ip at 30 min and in 20 mg/kg, ip at all testing intervals significantly except at 4 hrs, (n=10).

Drug and dose/kg, ip	*Mean onset time (min)*	*Mean cataleptic score ± SEM*					
		15 min	*30 min*	*1 hr*	*2 hr*	*3 hr*	*4 hr*
Control PPG (0.1 ml)	5.2	1.50 ± .19	1.88 ± .12	2.63 ± .18	2.87 ± .13	2.13 ± .13	1.25 ± .10
Nifedipine (5 mg)	5.5	1.38 ± .18	1.88 ± .18	2.38 ± .18	2.63 ± .18	2.14 ± .14	1.28 ± .13
Nifedipine (10 mg)	8.0	1.13 ± .13	1.38 ± .18*	2.25 ± .16	2.50 ± .19	1.88 ± .03	1.13 ± .13
Nifedipine (20 mg)	14.2	0.63 ± .18**	1.00 ± 00**	1.63 ± .18**	2.13 ± .13**	1.75 ± .16**	1.00 ± 00

PPG - Propyleneglycol; *P<0.05, **P<0.01.

TABLE V : Showing the effect of pretreatment with Verapamil on Methamphetamine-induced stereotypy. There is a significant inhibition of stereotypic score at all doses at 15 min and 30 min time interval and at 1 hr, 2 hr and 3 hr in the dose of 20 mg/kg, ip, (n=10).

Drug and dose/kg, ip	*Mean onset time (min)*	*Mean cataleptic score ± SEM*					
		15 min	*30 min*	*1 hr*	*2 hr*	*3 hr*	*4 hr*
Control DDW (0.1 ml)	5.9	1.50 ± .20	1.88 ± .13	2.38 ± .20	2.63 ± .20	2.00 ± .20	1.00 ± .00
Verapamil (5 mg)	6.5	1.20 ± .17*	1.25 ± .17**	2.25 ± .17	2.75 ± .17	2.25 ± .17	1.00 ± 00
Verapamil (10 mg)	8.0	1.00 ± 00*	1.38 ± .20*	2.26 ± .19	2.38 ± .20	2.00 ± 00	0.75 ± .17
Verapamil (20 mg)	13.9	0.63 ± .20**	1.00 ± 00**	2.00 ± .00**	2.38 ± .20**	1.60 ± .13**	0.63 ± .17

DDW - Double distilled water; *P<0.05, **P<0.01.

TABLE VI : Showing the effect of pretreatment with Diltiazem on Methamphetamine-induced stereotypy. There is a significant inhibition of stereotypic score in the dose of 20 mg/kg, ip at all time intervals, (n=10).

Drug and dose/kg, ip	*Mean onset time (min)*	*Mean cataleptic score ± SEM*					
		15 min	*30 min*	*1 hr*	*2 hr*	*3 hr*	*4 hr*
Control DDW (0.1 ml)	5.2	1.50 ± .19	2.00 ± 00	2.50 ± .19	2.88 ± .13	2.38 ± .18	1.25 ± .16
Diltiazem (5 mg)	5.8	1.38 ± .18	1.88 ± .12	2.50 ± .19	2.88 ± 1.3	2.25 ± .16	1.13 ± .23
Diltiazem (10 mg)	7.0	1.38 ± .18	1.75 ± .16	2.38 ± .18	2.63 ± .18	2.25 ± .16	1.13 ± .13
Diltiazem (20 mg)	14.0	0.88 ± .35*	1.25 ± .16**	2.00 ± .00*	2.25 ± .16*	2.00 ± 00*	0.75 ± .16*

DDW - Double distilled water; *P<0.05, **P<0.01.

DISCUSSION

From the results it is clear that Ca-channel blockers used in this study potentiated Haloperidol induced catalepsy, whereas Methamphetamine induced stereotypic behaviour was decreased by these drugs.

Neuroleptics like Haloperidol block postsynaptic striatal DA receptors leading to the functional lack of DA at the postsynaptic receptor sites (1). Verapamil also possess dopamine antagonist property in the brain (5). The potentiation in catalepsy could be due to complimentary action of Ca-channel blockers and haloperidol. Our results are in accordance with Goldstein (8), since one decreases the release of neurotransmitter dopamine and the other blocks its receptor at the post synaptic junction.

Methamphetamine-induced stereotypic behaviour is considered to be due to activation of postsynaptic striatal and mesolimbic dopaminergic receptors by the released DA. (2, 3). The present study shows that pre-treatment with drugs increases the time of onset and decreases the intensity of stereotypic behaviour. This action could be explained on the basis of i) DA release inhibiting action of Ca-channel blockers and ii) DA antagonistic action like verapamil (5).

Noradrenaline also plays an important role in the regulation of stereotypic behaviour. Increase in the noradrenaline concentration inhibit stereotypic behaviour whereas decrease in noradrenaline concentration enhance stereotypic behaviour in rats (9). Verapamil also enhances noradrenaline concentration through α-2 receptors (10). This action of verapamil may also contribute to the inhibition of stereotypic behaviour.

To conclude, our study suggests that Ca-channel blockers used, modify drug-induced cataleptic and stereotypic behaviours in rats possibly through dopaminergic and adrenergic mechanisms.

ACKNOWLEDGEMENTS

Authors are grateful to "Torrent Laboratories" Ahmedabad for supply of drugs.

REFERENCES

1. Seeman P. Brain Dopamine receptors. *Pharmacol Rev* 1980; 32 : 232.
2. Randrup A, Munkvad I. Pharmacology and Physiology of stereotyped behaviour. *J Psychiat Res* 1974; 11 : 1-10.
3. Seeman P. Brain Dopamine receptors. *Pharmacol Rev* 1980; 32 : 229-313.
4. Borison RL, Hitri A, Klawans HL, Diamond BI. A new model in schizophrenia : Behaviour and receptor binding studies. In catacholamines, Basic and Clinical Frontiers Eds Newyork Paragamon Press, 1979; 719-721.
5. Mc.Gee R, Scheneider JE. Inhibition of high affinity synaptosomal uptake systems by Verapamil. *Mol Pharmacol* 1979; 16 : 877-885.
6. Chattopadhyay RN, Das HN, Roy RK, Mandal S, Das AK, Kumar S. Maitra SK, Das MM. Comparative studies of effects of Calcium channel blockers on glucose tolarence in normal rats. *Indian J Pharmacol* 1993; 25 : 170-172.
7. Costall B, Naylor RJ. Mesolimbic involvement with behavioural effects indicating antipsychotic activity. *Eur J Pharmacol* 1974; 27 : 46-58.
8. Goldstein JA. Calcium and Neurotransmission Bio. *Psychiatry* 1984; 19 : 3 : 465-466.
9. Dickson SL, Gadie B, Tulloch IF. Differential effects of specific alfa adrenoreceptor antagonist on catecholamine mediated behaviours. *Br J Pharmacol* 1986; 89 : 872.
10. Galzin AM and Langer SJ. Presynaptic adfa adrenoreceptor antagonism by Verapamil but not by Diltiazem in rabbit hypothalamic slices. *Br J Pharmacol* 1983; 78 : 571-577.