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EFFECTS OF BUSPIRONE ON DOPAMINE DEPENDENT BEHAVIOURS IN RATS

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Abstract : Buspirone, a partial agonist of 5-hydroxytryptamine$_{1A}$ autoreceptors, selectively blocks presynaptic nigrostriatal D2 dopamine (DA) autoreceptors. At doses which antagonised action of apomorphine in biochemical presynaptic nigrostriatal D2 DA autoreceptor test systems buspirone neither induced catalepsy nor antagonised apomorphine – induced turning behaviour in rats indicating that at these doses buspirone does not block postsynaptic striatal D2 and D1 DA receptors. This study determines whether at high doses buspirone blocks postsynaptic striatal D2 and D1 DA receptors and provides behavioural evidence for selective blockade of presynaptic nigrostriatal D2 DA autoreceptors by smaller doses of buspirone.

We investigated in rats whether buspirone induces catalepsy and effect of its pretreatment on DA agonist induced oral stereotypies and on cataleptic effect of haloperidol and small doses (0.05, 0.1 mg/kg, ip) of apomorphine.

Buspirone at 1.25, 2.5, 5 mg/kg, ip neither induced catalepsy nor antagonised apomorphine stereotypy but did potentiate dexamphetamine stereotypy and antagonised cataleptic effect of haloperidol and small doses of apomorphine. Buspirone at 10, 20, 40 mg/kg, ip induced catalepsy and antagonised apomorphine and dexamphetamine stereotypies.

Our results indicate that buspirone at 1.25, 2.5, 5 mg/kg blocks only presynaptic nigrostriatal D2 DA autoreceptors while at 10, 20, 40 mg/kg, it blocks postsynaptic striatal D2 and D1 DA receptors. Furthermore, buspirone at 1.25, 2.5, 5 mg/kg by selectively blocking presynaptic nigrostriatal D2 DA autoreceptors, increases synthesis of DA and makes more DA available for release by dexamphetamine and during haloperidol – induced compensatory ‘feedback’ increase of nigrostriatal DAergic neuronal activity and thus potentiates dexamphetamine stereotypy and antagonizes haloperidol catalepsy.

Key words : buspirone apomorphine dexamphetamine haloperidol stereotypy catalepsy rat

INTRODUCTION

The anxiolytic drug buspirone acts as a partial agonist at 5-hydroxytryptamine (5-HT, serotonin) 5-HT$_{1A}$ autoreceptors and as an antagonist at certain postsynaptic 5-HT$_{1A}$ receptors (1). Buspirone is also reported to preferentially block the presynaptic rather

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than the postsynaptic D2 dopamine (DA) receptors (2, 3, 4).

McMillen et al (3) have reported that buspirone antagonised the action of apomorphine in two biochemical presynaptic D2 DA autoreceptor test systems at doses which failed to induce catalepsy and to antagonize the postsynaptic striatal D2 DA receptor mediated apomorphine-induced turning behaviour in rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of the substantia nigra.

The neuroleptic haloperidol is nearly equieffective in blocking the pre and postsynaptic D2 DA receptors (5). The neuroleptic molindone and the antiemetic drug metoclopramide however, in smaller doses selectively block the presynaptic nigrostriatal D2 DA autoreceptors (6, 7) while at higher doses they block postsynaptic striatal D2 DA receptors in rats and antagonize apomorphine stereotypy and induce catalepsy (8, 9, 10). Since the selective presynaptic nigrostriatal D2 DA autoreceptor blockers molindone and metoclopramide at high doses block the postsynaptic striatal D2 DA receptors we presume that buspirone at high doses might also exhibit postsynaptic striatal D2 DA receptor blocking activity.

The present behavioural study was undertaken in rats to determine whether high doses of buspirone block the postsynaptic striatal D2 DA receptors and to provide behavioural evidence for the selective blockade of the presynaptic nigrostriatal D2 DA autoreceptors by smaller doses of buspirone which per se do not block the postsynaptic striatal D2 DA receptors. To achieve our objectives we have investigated the effects of pretreatment with a wide dose-range of buspirone on behaviours dependent on the functional status of the nigrostriatal DAergic system viz high – dose apomorphine and dexamphetamine – induced stereotyped behaviour (SB) of the oral movement variety and on catalepsy induced by small doses of apomorphine and by haloperidol. Further, we have investigated whether buspirone induces catalepsy.

Apomorphine in high doses elicits the oral movement variety (OMV) of SB (viz biting, gnawing or licking behaviour) in rats by directly stimulating the postsynaptic striatal D2 and D1 DA receptors (11). The intensity of apomorphine stereotypy therefore depends on the functional status of the postsynaptic striatal D2 and D1 DA receptors (11). High doses of dexamphetamine induce SB of the OMV in rats by releasing DA from the nigrostriatal DAergic neurons with resultant activation by the released DA of postsynaptic striatal D2 and D1 DA receptors (11, 12). The intensity of dexamphetamine stereotypy therefore depends on the synthesis of DA and the intraneuronal stores of DA available for release by dexamphetamine, in addition to the functional status of the postsynaptic striatal D2 and D1 DA receptors (11, 12). Catalepsy in animals is attributed to a functional lack of DA at postsynaptic striatal D2 and D1 DA receptor sites. Haloperidol induces catalepsy by blocking the postsynaptic striatal D2 and D1 DA receptors (13). Small doses of apomorphine selectively stimulate the presynaptic nigrostriatal D2 DA autoreceptors and induce long-lasting inhibition of DA synthesis and release (14, 15). They thus produce a lack of DA at postsynaptic striatal D2 and D1 DA receptor sites with resultant catalepsy in rats (16). The SB induced by high doses of apomorphine has a rapid onset and is short lasting because

of rapid apomorphine metabolism. In contrast, the small dose apomorphine induced catalepsy has a comparatively delayed onset and is long lasting (16).

MATERIAL AND METHODS

Animals

Male Wistar rats (100–180 g) bred in the Central Animal House facility of the Institute were used. The animals were housed under standard conditions, maintained on a 12 h light – dark cycle and had free access to food and water upto the time of experimentation. The animals were brought to the department and kept in a noiseless diffusely illuminated laboratory, atleast 1 h before the experiments for acclimatization to the laboratory environment. Animals were randomly distributed into groups of 10 animals each. Each animal was used only once. All observations were made between 10 and 16 h at 27–30°C. Observations were made blind with respect to the treatments used. The protocol of the study was approved by the Institutional Animal Ethics Committee and the care of the animals was as per the 'Guidelines for the Care and Use of Animals in Scientific Research' prepared by the Indian National Science Academy, New Delhi.

Drugs and solutions

Buspirone HC1 (Courtesy, Merind Ltd. India) and dexamphetamine sulfate (Koch-light UK) were dissolved in distilled water while apomorphine HC1 (Sigma U.S.A.) was dissolved in distilled water containing 0.2 mg/ml ascorbic acid. Haloperidol (Sun Pharmaceuticals Ltd. India) injection solution was diluted to required strength with distilled water. All drug solutions were prepared immediately before use and were injected intraperitoneally in a volume of 2 ml/kg body weight. Doses refer to the forms mentioned. Drug doses and the testing time intervals were selected based on previous studies conducted in our laboratory and those reported in literature.

High dose apomorphine and dexamphetamine induced SB in rats

The rats were placed in individual cages made of wire netting, measuring 30 × 20 × 20 cm, 30 min before drug or distilled water treatment to allow adaptation to the new environment. Following administration of apomorphine (1.5 and 3 mg/kg) or dexamphetamine (5 and 10 mg/kg), the intensity of SB was assessed over a 30 s observation period at 10 min intervals, using the scoring system of Costall and Naylor (17) where periodic sniffing = score 1, continuous sniffing = 2, periodic biting, gnawing or licking = 3 and continuous biting, gnawing or licking = 4. Inter-rater reliability was calculated from those simultaneous ratings made by two of the authors using the Pearson product-moment correlation (r). Inter-rater correlation coefficient r was found to be 0.96, indicating a high degree of inter-rater agreement. The cumulative stereotyped rating for each animal was determined as the sum of each 10 min score for 90 min for apomorphine-induced SB or 180 min for dexamphetamine – induced SB. The cumulative stereotypy score of each rat in the group was taken to compute the median value of the group. Buspirone (0.625 to 40 mg/kg) or haloperidol (0.5 mg/kg) was injected 1 h before apomorphine or dexamphetamine while the control groups received 2 ml/kg body weight of distilled water ip 1 h before receiving the DA agonists.

Catalepsy testing in rats

Rats were tested for catalepsy according to the method of Costall and Naylor (17) by placing both front paws of the animal over an 8 cm high horizontal bar and measuring the time that the animal maintained the imposed posture. Animals maintaining the imposed posture for more than 10 s were considered to be cataleptic. Animals were tested for catalepsy 0.5, 1, 2 and 3 h after ip injection of buspirone (0.625 to 40 mg/kg), haloperidol (1 mg/kg) or distilled water (2 ml/kg body weight).

Small dose apomorphine and haloperidol induced catalepsy in rats

Buspirone (0.625, 1.25, 2.5 and 5 mg/kg) was injected 1 h before small doses of apomorphine (0.05 and 0.1 mg/kg) or haloperidol (0.5 and 1 mg/kg). Control groups received 2 ml/kg body weight of distilled water ip 1 h before receiving apomorphine or haloperidol. Animals were evaluated for catalepsy 1 and 2 h after apomorphine or haloperidol treatment by placing both front paws of the animal over an 8 cm high horizontal bar. The time elapsing between paw placement and the first movement of either paw (descent latency) was measured in seconds. Catalepsy score (descent latency in seconds) of each animal in the group, at the respective testing time interval, was taken to compute the mean value of the group for that particular timing.

Statistical analysis

The results pertaining to the effects of drugs on DA agonist induced SB were analysed by the two-tailed Mann-Whitney U-test for non-parametric data using the individual cumulative stereotypy score. The results concerning effects of buspirone pretreatment on catalepsy induced by small doses of apomorphine and haloperidol were analysed by the two-tailed Student's unpaired t-test. A P value less than 0.05 was considered as statistically significant.

RESULTS

In preliminary experiments it was observed that animals receiving 0.625, 1.25, 2.5 and 5 mg/kg, ip doses of buspirone did not exhibit any gross behavioural changes and appeared the same as distilled water (2 ml/kg, ip) treated control animals. Buspirone, in the dose range of 10 to 40 mg/kg, ip, reduced motor activity, animals appeared sedated but did not exhibit motor incoordination, muscular hyptonia or ataxia. Further, in the dose range of 0.625 to 40 mg/kg, ip, buspirone did not induce postsynaptic 5-HT_{1A} receptor mediated behavioural syndrome or the 5-HT_{2A} receptor mediated wet-dog shake behaviour or any feature of DA agonist induced SB of the OMV in rats. As doses beyond 40 mg/kg, ip had induced clonic convulsions and mortality, for subsequent studies buspirone was therefore used in the dose range of 0.625 to 40 mg/kg, ip.

1. Effect on high dose apomorphine induced SB in rats

Table I shows the effect of pretreatment with buspirone and haloperidol on apomorphine induced SB in rats. Pretreatment with 0.625, 1.25, 2.5 and 5 mg/kg buspirone did not significantly influence apomorphine (1.5 and 3 mg/kg) induced SB. The median SB scores of the groups pretreated with 0.625, 1.25, 2.5 and 5 mg/kg buspirone did not differ significantly from the median SB score of their distilled water pretreated control 1.5 mg/kg apomorphine

TABLE I: Effect of buspirone (BUS) and haloperidol (HAL) pretreatment on apomorphine (APO) induced stereotyped behaviour in rats.

Study	*Group (n=10)*	*Treatment (mg/kg, ip)*	*Median SB score (with ranges)*
I. A.	1.	DW + APO (1.5)	10.5 (9-12)
	2.	BUS (0.625) + APO (1.5)	10.5 (9-13)
	3.	BUS (1.25) + APO (1.5)	11.0 (10-13)
	4.	BUS (2.5) + APO (1.5)	10.5 (10-12)
	5.	BUS (5) + APO (1.5)	10.0 (8-12)
	6.	BUS (10) + APO (1.5)	4.5 (3-6)*
	7.	BUS (20) + APO (1.5)	0.0
B.	1.	DW + APO (3)	17.0 (16-19)
	2.	BUS (0.625) + APO (3)	16.5 (15-19)
	3.	BUS (1.25) + APO (3)	17.5 (16-20)
	4.	BUS (2.5) + APO (3)	17.0 (15-19)
	5.	BUS (5) + APO (3)	16.5 (16-18)
	6.	BUS (10) + APO (3)	11.0 (10-13)*
	7.	BUS (20) + APO (3)	5.0 (4-7)**
	8.	BUS (40) + APO (3)	0.0
II. A.	1.	DW + APO (1.5)	10.0 (9-13)
	2.	HAL (0.5) + APO (1.5)	0.0
B.	1.	DW + APO (3)	16.5 (15-19)
	2.	HAL (0.5) + APO (3)	0.0

*P<0.01, **P<0.001 as compared to the respective distilled water pretreated control apomorphine group by Mann-Whitney's U-test.

DW=Distilled water (2 ml/kg, ip).

group (10.5, 11, 10.5 and 10 respectively vs 10.5, P>0.05, Study IA) and 3 mg/kg apomorphine group (16.5, 17.5, 17 and 16.5 respectively vs 17, P>0.05, Study IB). However, pretreatment with 10 mg/kg buspirone caused a significant decrease in the median SB score as compared to its distilled water pretreated control 1.5 mg/kg apomorphine group (4.5 vs 10.5, P<0.01, Study IA) and 3 mg/kg apomorphine group (11 vs 17, P<0.01, Study IB). Further, animals pretreated with 20 mg/kg buspirone did not exhibit SB following administration of 1.5 mg/kg apomorphine, the median SB score of the group being zero as compared to 10.5 of its distilled water pretreated control 1.5 mg/kg apomorphine group (Study IA). Pretreatment with 20 mg/kg buspirone caused a significant decrease in the median SB score as compared to its distilled water pretreated control 3 mg/kg apomorphine group (5 vs 17, P<0.001, Study IB). Animals pretreated with 40 mg/kg buspirone did not exhibit SB following administration of 3 mg/kg apomorphine, the median SB score of the group being zero as compared to 17 of its distilled-water pretreated control 3 mg/kg apomorphine group (Study IB).

Animals pretreated with 0.5 mg/kg haloperidol did not exhibit SB following administration of 1.5 and 3 mg/kg apomorphine, the median SB score of the two groups being zero as compared to 10 and 16.5 of their respective distilled water pretreated control 1.5 and 3 mg/kg apomorphine groups (Study II A and B, respectively).

2. Effect on dexamphetamine induced SB in rats

Table II shows the effect of pretreatment with buspirone and haloperidol on dexamphetamine induced SB in rats. Pretreatment with 0.625 mg/kg buspirone did not cause a significant increase (21.5 vs 20, P>0.05) whereas pretreatment with 1.25, 2.5 and 5 mg/kg buspirone caused a significant increase in the median SB score as compared to their distilled water pretreated control 5 mg/kg dexamphetamine group (23.5, 27 and 31 respectively vs 20, P<0.05, P<0.01 and P<0.001 respectively, Study IA). However, pretreatment with 10 and 20 mg/kg buspirone caused a significant decrease in the median SB score as compared to their distilled water pretreated control 5 mg/kg dexamphetamine group (15.5 and 8 respectively vs 20, P<0.02 and P<0.001 respectively, Study IA). Further, animals pretreated with 40 mg/kg buspirone did not

TABLE II : Effect of buspirone (BUS) and haloperidol (HAL) pretreatment on dexamphetamine (DAM) induced stereotyped behaviour in rats.

Study Group (n=10)		*Treatment (mg/kg, ip)*	*Median SB score (with ranges)*
I. A.	1.	DW + DAM (5)	20.0 (18-23)
	2.	BUS (0.625) + DAM (5)	21.5 (17-22)
	3.	BUS (1.25) + DAM (5)	23.5 (22-26)*
	4.	BUS (2.5) + DAM (5)	27.0 (26-29)***
	5.	BUS (5) + DAM (5)	31.0 (29-34)****
	6.	BUS (10) + DAM (5)	15.5 (14-18)**
	7.	BUS (20) + DAM (5)	8.0 (6-10)****
	8.	BUS (40) + DAM (5)	0.0
B.	1.	DW + DAM (10)	36.5 (34-38)
	2.	BUS (0.625) + DAM (10)	38.0 (33-39)
	3.	BUS (1.25) + DAM (10)	40.0 (38-42)*
	4.	BUS (2.5) + DAM (10)	43.5 (41-45)***
	5.	BUS (5) + DAM (10)	47.5 (45-49)****
	6.	BUS (10) + DAM (10)	32.0 (30-34)**
	7.	BUS (20) + DAM (10)	24.5 (22-26)****
	8.	BUS (40) + DAM (10)	14.5 (12-16)****
II. A.	1.	DW + DAM (5)	20.5 (18-22)
	2.	HAL (0.5) + DAM (5)	0.0
B.	1.	DW + DAM (10)	37.0 (34-39)
	2.	HAL (0.5) + DAM (10)	14.0 (11-16)****

*P<0.05, **P<0.02, ***P<0.01, ****P<0.001 as compared to the respective distilled water pretreated control dexamphetamine group by Mann-Whitney's U-test.

DW=Distilled water (2 ml/kg, ip).

exhibit SB following administration of 5 mg/kg dexamphetamine, the median SB score of the group being zero as compared to 20 of its distilled water pretreated control 5 mg/kg dexamphetamine group (Study IA).

Pretreatment with 0.625 mg/kg buspirone did not cause a significant increase (38 vs 36.5, P>0.05) whereas pretreatment with 1.25, 2.5 and 5 mg/kg buspirone caused a significant increase in the median SB score as compared to their distilled water pretreated control 10 mg/kg dexamphetamine group (40, 43.5 and 47.5 respectively vs 36.5, P<0.05, P<0.01 and P<0.001 respectively, Study IB). However, pretreatment with 10, 20 and 40 mg/kg buspirone caused a significant decrease in the median SB score as compared to their distilled water pretreated control 10 mg/kg dexamphetamine group (32, 24.5 and 14.5 respectively vs 36.5, P<0.02, P<0.001 and P<0.001 respectively, Study IB).

Animals pretreated with 0.5 mg/kg haloperidol did not exhibit SB following administration of 5 mg/kg dexamphetamine, the median SB score of the group being zero as compared to 20.5 of its distilled water pretreated control 5 mg/kg dexamphetamine group (Study IIA). Further, pretreatment with 0.5 mg/kg haloperidol caused a significant decrease in the median SB score as compared to its distilled water pretreated control 10 mg/kg dexamphetamine group (14 vs 37, P<0.001, Study IIB).

3. Catalepsy induced by buspirone and haloperidol in rats

Buspirone (0.625, 1.25, 2.5 and 5 mg/kg) and distilled water (2 ml/kg body weight) treated rats were considered not to be cataleptic as they failed to maintain the imposed posture for more than 3 s at any of the testing time intervals. However, 70%, 90% and 100% of the animals treated with 10, 20 and 40 mg/kg doses of buspirone respectively (n=10 for each dose) and 100% of the animals treated with 1 mg/kg haloperidol (n=10) maintained the imposed posture for more than 10 s at each testing time interval and hence were considered to be cataleptic.

4. Effect on small dose apomorphine and haloperidol induced catalepsy in rats

Table III shows the effect of pretreatment with buspirone on catalepsy induced by small doses of apomorphine and haloperidol in rats. Pretreatment with 0.625 mg/kg buspirone did not cause a significant decrease in the

TABLE III: Effect of buspirone (BUS) pretreatment on catalepsy induced by small doses of apomorphine (APO) and haloperidol (HAL) in rats.

Study	*Group (n=10)*	*Treatment (mg/kg, ip)*	*Catalepsy score (descent latency in seconds; Mean±SEM)*	
			1 h	*2 h*
I. A.	1.	DW + APO (0.05)	28.2±1.32	35.9±1.37
	2.	BUS (0.625) + APO (0.05)	26.0±1.23	33.6±1.31
	3.	BUS (1.25) + APO (0.05)	19.7±1.22***	27.5±1.28***
	4.	BUS (2.5) + APO (0.05)	15.6±1.18****	23.3±1.24****
	5.	BUS (5) + APO (0.05)	12.8±1.12****	20.7±1.22****
B.	1.	DW + APO (0.1)	52.6±1.75	60.6±1.81
	2.	BUS (0.625) + APO (0.1)	50.5±1.51	58.4±1.79
	3.	BUS (1.25) + APO (0.1)	44.1±1.46**	52.0±1.51**
	4.	BUS (2.5) + APO (0.1)	40.3±1.42***	48.1±1.47***
	5.	BUS (5) + APO (0.1)	37.2±1.39****	45.2±1.44****
II. A.	1.	DW + HAL (0.5)	34.6±1.35	28.7±1.30
	2.	BUS (0.625) + HAL (0.5)	32.5±1.29	26.5±1.25
	3.	BUS (1.25) + HAL (0.5)	29.1±1.26*	23.2±1.23*
	4.	BUS (2.5) + HAL (0.5)	24.9±1.27***	18.9±1.21***
	5.	BUS (5) + HAL (0.5)	20.1±1.22****	14.2±1.16****
B.	1.	DW + HAL (1)	58.2±1.58	52.4±1.53
	2.	BUS (0.625) + HAL (1)	55.9±1.54	50.2±1.48
	3.	BUS (1.25) + HAL (1)	52.8±1.52*	46.9±1.44*
	4.	BUS (2.5) + HAL (1)	48.7±1.47***	42.8±1.41***
	5.	BUS (5) + HAL (1)	43.9±1.45****	38.0±1.39****

**P<0.02, ***P<0.01, ****P<0.001 as compared to the respective distilled water pretreated control apomorphine or haloperidol group, at the respective testing time interval, by Student's unpaired t-test.

DW=Distilled water (2 ml/kg, ip).

catalepsy score, at both 1 h and 2 h testing time interval, as compared to its distilled water pretreated control 0.05 mg/kg apomorphine group (26.0±1.23 vs 28.2±1.32 at 1 h and 33.6±1.31 vs 35.9±1.37 at 2 h testing time interval, Study IA). However, pretreatment with 1.25, 2.5 and 5 mg/kg buspirone caused a significant decrease in the catalepsy score, at both 1 h and 2 h testing time interval, as compared to their distilled water pretreated control 0.05 mg/kg apomorphine group (19.7±1.22, 15.6±1.18 and 12.8±1.12 respectively vs 28.2±1.32 at 1 h, P<0.01, P<0.001 and P<0.001 respectively; and 27.5±1.28, 23.3±1.24 and 20.7±1.22 respectively vs 35.9±1.37 at 2 h testing time interval, P<0.01, P<0.001 and P<0.001 respectively, Study IA). Similarly, pretreatment with 0.625 mg/kg buspirone did not cause a significant decrease in the catalepsy score, at both 1 h and 2 h testing time interval, as compared to its distilled water pretreated control 0.1 mg/kg apomorphine group (50.5±1.51 vs 52.6±1.75 at 1 h and 58.4±1.79 vs 60.6±1.81 at 2 h testing time interval, Study IB). However, pretreatment with 1.25, 2.5 and 5 mg/kg buspirone caused a significant decrease in the catalepsy score, at both 1 h and 2 h testing time interval, as compared to their distilled water pretreated control 0.1 mg/kg apomorphine group (44.1±1.46, 40.3±1.42 and 37.2±1.39 respectively vs 52.6±1.75 at 1 h, P<0.02, P<0.01 and P<0.001 respectively; and 52.0±1.51, 48.1±1.47 and 45.2±1.44 respectively vs 60.6±1.81 at 2 h testing time interval, P<0.02, P<0.01 and P<0.001 respectively, Study IB).

Pretreatment with 0.625 mg/kg buspirone did not cause a significant decrease in the catalepsy score, at both 1 h and 2 h testing time interval, as compared to its distilled water pretreated control 0.5 mg/kg haloperidol group (32.5±1.29 vs 34.6±1.35 at 1 h and 26.5±1.25 vs 28.7±1.30 at 2 h testing time interval, Study IIA). However, pretreatment with 1,25, 2.5 and 5 mg/kg buspirone caused a significant decrease in the catalepsy score, at both 1 h and 2 h testing time interval, as compared to their distilled water pretreated control 0.5 mg/kg haloperidol group (29.1±1.26, 24.9±1.27 and 20.1±1.22 respectively vs 34.6±1.35 at 1 h, $P<0.05$, $P<0.01$ and $P<0.001$ respectively; and 23.2±1.23, 18.9±1.21 and 14.2±1.16 respectively vs 28.7±1.30 at 2 h testing time interval, $P<0.05$, $P<0.01$ and $P<0.001$ respectively, Study IIA). Similarly, pretreatment with 0.625 mg/kg buspirone did not cause a significant decrease in the catalepsy score, at both 1 h and 2 h testing time interval, as compared to its distilled water pretreated control 1 mg/kg haloperidol group (55.9±1.54 vs 58.2±1.58 at 1 h and 50.2±1.48 vs 52.4±1.53 at 2 h testing time interval, Study IIB). However, pretreatment with 1.25, 2.5 and 5 mg/kg buspirone caused a significant decrease in the catalepsy score at both 1 h and 2 h testing time interval, as compared to their distilled water pretreated control 1 mg/kg haloperidol group (52.8±1.52, 48.7±1.47 and 43.9±1.45 respectively vs 58.2±1.58 at 1 h, $P<0.05$, $P<0.01$ and $P<0.001$ respectively; and 46.9±1.44, 42.8±1.41 and 38.0±1.39 respectively vs 52.4±1.53 at 2 h testing time interval, $P<0.05$, $P<0.01$ and $P<0.001$ respectively, Study IIB).

The effect of pretreatment with 10, 20 and 40 mg/kg buspirone on catalepsy induced by small doses of apomorphine and haloperidol was not studied as, at these doses, buspirone itself had induced catalepsy in rats.

DISCUSSION

Haloperidol induces catalepsy and antagonises apomorphine induced SB of OMV in rats by blocking the postsynaptic striatal D2 and D1 DA receptors (11, 13). In addition, following the blockade of the pre- and postsynaptic nigrostriatal D2 DA receptors by haloperidol, there is a compensatory 'feed-back' increase of nigrostriatal DAergic neuronal activity, which is associated with an allosteric activation of tyrosine hydroxylase. Consequently, there is an increase in the synthesis and release of DA which counteracts, to some extent, the haloperidol-induced blockade of the postsynaptic striatal D2 and D1 DA receptors (15).

In the present study treatment with 0.625, 1.25, 2.5 and 5 mg/kg buspirone did not induce catalepsy and pretreatment with these doses of buspirone failed to antagonize apomorphine induced SB of OMV in rats. However, at higher doses viz 10, 20 and 40 mg/kg buspirone did induce catalepsy and pretreatment with these doses of buspirone antagonised apomorphine induced OMV of SB in rats. Our results indicate that buspirone at 0.625–5 mg/kg does not block the postsynaptic striatal D2 and D1 DA receptors while at 10, 20 and 40 mg/kg doses buspirone exerts postsynaptic striatal D2 and D1 DA receptor blocking activity. As 10, 20 and 40 mg/kg doses of buspirone block the postsynaptic striatal D2 and D1 DA receptors pretreatment with these doses of buspirone therefore antagonised the OMV of SB induced by the DA releaser dexamphetamine.

Our findings with buspirone at 0.625–5 mg/kg ip and the conclusions derived thereoff are in agreement with those of McMillen et al (3). These authors have reported that buspirone in the dose range of 1–5 mg/kg ip did not induce catalepsy and pretreatment with 1–5 mg/kg ip buspirone did not antagonise apomorphine–induced turning behaviour in rats with unilateral 6-OHDA lesions of substantia nigra. Based on their observations McMillen et al (3) concluded that at 1–5 mg/kg ip buspirone does not block the postsynaptic striatal D2 DA receptors. Further, our observation that pretreatment with 0.625–5 mg/kg, ip buspirone failed to antagonize whereas pretreatment with 10, 20 and 40 mg/kg, ip buspirone antagonised apomorphine-induced OMV of SB in rats concurs with the finding of Skolnick et al (18). These authors have reported that pretreatment with 5 mg/kg, ip buspirone failed to antagonize whereas pretreatment with 10 and 20 mg/kg, ip buspirone antagonised apomorphine (2 mg/kg, ip)–induced OMV of SB in rats. Thus their finding supports our contention that at 10, 20 and 40 mg/kg ip buspirone blocks the postsynaptic striatal D2 and D1 DA receptors.

Buspirone has been reported to displace [^{3}H] spiperidol from rat striatal binding sites with an IC_{50} of 1.8×10^{-7} M as compared to 4.7×10^{-9} M IC_{50} of haloperidol and also to be a weak inhibitor of DA-stimulated adenyl cyclase (19). Our behavioural study thus demonstrates that buspirone, at 10, 20 and 40 mg/kg, acts as an antagonist at the postsynaptic striatal D2 and D1 DA receptor sites and also that on weight basis it is much less potent than haloperidol in inducing catalepsy and antagonising apomorphine stereotypy in rats.

The neuroleptic haloperidol, by blocking the postsynaptic striatal D2 DA receptors, worsens Parkinsonian condition (20). Further, long-term administration of haloperidol to psychotic patients, by increasing the number and sensitivity of postsynaptic striatal D2 DA receptors, induces the late-appearing neurological syndrome termed tardive dyskinesia (20). Increasing the dose of haloperidol tends to suppress the manifestations of tardive dyskinesia by blocking the supersensitive postsynaptic striatal D2 DA receptors (20). Our finding that buspirone, at high doses viz 10, 20 and 40 mg/kg blocks the postsynaptic striatal D2 DA receptors readily explains the clinical observations that buspirone, at doses higher than the conventional anxiolytic doses, caused worsening of parkinsonian symptoms (21, 22) and high doses of buspirone were efficacious in the treatment of tardive dyskinesia (22). Further, acute administration of buspirone abolished the expression of behavioural DAergic supersensitivity in mice withdrawn from chronic haloperidol treatment (23).

In the present study pretreatment with 1.25, 2.5 and 5 mg/kg doses of buspirone, which do not block the postsynaptic striatal D2 and D1 DA receptors, did potentiate dexamphetamine stereotypy and antagonised catalepsy induced by small doses of apomorphine and haloperidol. Since pretreatment with 1.25, 2.5 and 5 mg/kg buspirone had not potentiated apomorphine stereotypy, it suggests that potentiation of dexamphetamine stereotypy and antagonism of haloperidol catalepsy by 1.25, 2.5 and 5 mg/kg buspirone is not due to any facilitatory effect of these doses of buspirone at or beyond the postsynaptic striatal D2 and D1 DA receptor sites.

Small doses of apomorphine, via selective stimulation of the presynaptic nigrostriatal D2 DA autoreceptors, induce catalepsy in rats (16). In the present study pretreatment with 1.25, 2.5 and 5 mg/kg, ip doses of buspirone antagonised the cataleptic effect of small doses of apomorphine. Thus the overall findings of our study indicate that at 1.25, 2.5 and 5 mg/kg buspirone selectively blocks the presynaptic nigrostriatal D2 DA autoreceptors without blocking the postsynaptic striatal D2 and D1 DA receptors. Our finding that buspirone at 1.25, 2.5 and 5 mg/kg antagonised the cataleptic effect of small doses of apomorphine concurs with the observations of McMillen et al (3). These authors have reported that buspirone in the dose range of 1–5 mg/kg, which did not exert postsynaptic striatal D2 DA receptor blocking activity however, did block the inhibitory action of apomorphine in two biochemical DA autoreceptor test systems i.e. blocked the inhibitory action of apomorphine on synaptosomal tyrosine hydroxylase activity in vitro preparations and in vivo the y-butyrolactone-induced activation of striatal tyrosine hydroxylase.

Neuroleptics, by blocking the presynaptic nigrostriatal D2 DA autoreceptors, increase the intraneuronal synthesis of DA and thereby increase the intraneuronal stores of DA (15). Potentiation of dexamphetamine stereotypy and antagonism of haloperidol catalepsy by pretreatment with 1.25, 2.5 and 5 mg/kg, ip doses of buspirone is explained on the basis of buspirone (1.25, 2.5, 5 mg/kg, ip)–induced selective blockade of the presynaptic nigrostriatal D2 DA autoreceptors. We postulate that 1.25, 2.5 and 5 mg/kg doses of buspirone, by blocking the presynaptic nigrostriatal D2 DA autoreceptors, increase the intraneuronal synthesis and stores of DA and make more DA available for release by dexamphetamine from the nigrostriatal DAergic neurons. Since at these doses buspirone does not block the postsynaptic striatal D2 and D1 DA receptors the excessive dexamphetamine – induced release of DA from the nigrostriatal DAergic neurons results in potentiation of dexamphetamine stereotypy. Likewise, as more DA is available for release during the haloperidol – induced compensatory 'feed-back' increase of nigrostriatal DAergic neuronal activity, the haloperidol – induced blockade of the postsynaptic striatal D2 and D1 DA receptors is counteracted to a greater extent, with resultant antagonism of haloperidol catalepsy. Furthermore, Conway and Uretsky (24) and Howard et al (25) had also explained the enhancement of amphetamine stereotypy in rats by small doses of molindone (24) and by small doses of metoclopramide (25) on the basis of selective blockade of the presynaptic nigrostriatal D2 DA autoreceptors by the small doses of these drugs (6, 7).

Amphetamine–induced SB in animals, because of its similarity to abnormal behaviour observed during amphetamine psychosis in humans and in schizophrenics, is considered to be one of the DA related animal models of paranoid schizophrenia (26). In our study pretreatment with 1.25, 2.5 and 5 mg/kg doses of buspirone, by blocking the presynaptic nigrostriatal D2 DA autoreceptors, enhanced DAergic neurotransmission and potentiated dexamphetamine stereotypy. Our finding suggests that there is a possibility of buspirone inducing psychosis especially in psychosis-prone individuals. Our suggestion is supported by clinical reports stating that buspirone at anxiolytic doses has induced psychotic reactions especially in psychosis-prone individuals (22).

Our findings, that buspirone at smaller doses viz 1.25, 2.5 and 5 mg/kg, ip selectively blocks the presynaptic nigrostriatal D2 DA autoreceptors whereas it blocks the postsynaptic striatal D2 and D1 DA receptors only at higher doses ie 10, 20 and 40 mg/kg, ip, do not concur with the findings of Conceicao and Frussa-Filho (27). These authors have reported that pretreatment with 0.1 to 3 mg/kg buspirone administered sc 30 min before the testing antagonised apomorphine (0.06 mg/kg, sc)–induced yawning and also apomorphine (1 mg/kg, sc) – induced stereotypy in rats. Low dose apomorphine – induced yawning results from activation of presynaptic nigrostriatal D2 DA autoreceptors by apomorphine (28) whereas apomorphine stereotypy results from direct stimulation of postsynaptic striatal D2 and D1 DA receptors by apomorphine (11). The results of Conceicao and Frussa-Filho (27) therefore, indicate that buspirone is equieffective in blocking the pre- and postsynaptic nigrostriatal D2 DA receptors and are contradictory to our findings and those of other workers (2, 3, 4, 18). Further, in our study, 1 h pretreatment with 1.25, 2.5 and 5 mg/kg, ip doses of buspirone, which selectively block the presynaptic nigrostriatal D2 DA autoreceptors, antagonised haloperidol (1 mg/kg, ip)–induced catalepsy. In the study of Conceicao and Frussa-Filho (27) 30 min pretreatment with 0.1 to 3 mg/kg, sc doses of buspirone, which block both pre- and postsynaptic nigrostriatal D2 DA receptors, antagonized haloperidol (2 mg/kg, ip)–induced catalepsy. Though there are differences in the routes of administration of buspirone (ip vs sc) and pretreatment timing intervals (1 h vs 30 min) between our study and that of Conceicao and Frussa-Filho (27) we doubt whether they can account for the contradictory findings. At present we are not in a position to explain the discrepancy between our findings and those of Conceicao and Frussa-Filho (27).

To conclude, the findings of our present study indicate that buspirone exerts dose-dependent opposite effects on the functioning of the nigrostriatal DAergic system. At lower doses viz 1.25, 2.5 and 5 mg/kg, ip, buspirone, by selectively blocking the presynaptic nigrostriatal D2 DA autoreceptors, increases the intraneuronal synthesis of DA and by making more DA available for release enhances nigrostriatal DAergic neurotransmission. Buspirone at higher doses viz 10, 20 and 40 mg/kg, ip by blocking the postsynaptic striatal D2 and D1 DA receptors however, causes hypofunctioning of the nigrostriatal DAergic system.

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