



studies indicate that 5-HT inhibits the synthesis and release of dopamine (DA) from rat nigrostriatal DAergic neurons by stimulating the 5-HT<sub>2A/2C</sub> receptors located on the DA cell bodies and axonal terminals (2, 3). Further, behavioural studies in animals have demonstrated that drugs which affect central 5-HTergic neurotransmission modulate the intensity of behaviours dependent on the functional status of the nigrostriatal DAergic system viz DA agonist induced stereotyped behaviour (SB) (4, 5, 6) and neuroleptic induced catalepsy (7, 8, 9).

The anorectic dexfenfluramine, on acute administration, enhances central 5-HTergic neurotransmission by causing a rapid release of 5-HT from brain 5-HTergic neurons (10, 11). The present study was undertaken in rats to determine whether dexfenfluramine, through the released 5-HT, modulates the intensity of the oral movement variety of SB induced by apomorphine and dexamphetamine and the intensity of catalepsy induced by haloperidol and small doses of apomorphine. Further, we have investigated whether dexfenfluramine induces catalepsy in rats.

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 (12). The intensity of apomorphine stereotypy therefore depends on the functional status of the postsynaptic striatal D2 and D1 DA receptors (12). High doses of dexamphetamine induce SB of the OMV in rats by releasing DA from the nigrostriatal DAergic neurons with resultant stimulation

of the postsynaptic striatal D2 and D1 DA receptors by the released DA (12, 13). 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 (12, 13). 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 (14). Small doses of apomorphine selectively stimulate the presynaptic nigrostriatal D2 DA autoreceptors and induce long-lasting inhibition of DA synthesis and release (15, 16). They thus produce a lack of DA at postsynaptic striatal D2 and D1 DA receptor sites with resultant catalepsy in rats (17). 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 (17).

## 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 2 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 by an experimenter who was unaware of the animal's treatment. 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**

Dexfenfluramine HCl (Courtesy, Wockhardt Ltd India) and dexamphetamine sulfate (Koch-light UK) were dissolved in distilled water while apomorphine HCl (Sigma U.S.A.) was dissolved in distilled water containing 0.2 mg/ml ascorbic acid. Haloperidol (Searle India) injection solution was diluted to required strength with distilled water. Doses refer to the forms mentioned. All drug solutions were prepared immediately before use and were injected intraperitoneally in a volume of 2 ml/kg body weight.

#### **Dexamphetamine and high dose apomorphine 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 dexamphetamine or apomorphine the intensity of SB was assessed over a 30 s observation period at 10 min intervals, using the scoring system of Costall and Naylor

(18) where periodic sniffing = score 1, continuous sniffing = 2, periodic biting, gnawing or licking = 3 and continuous biting, gnawing or licking = 4. The cumulative stereotyped rating for each animal was determined as the sum of each 10 min score for 180 min for dexamphetamine-induced stereotypy or 90 min for apomorphine-induced SB. The cumulative stereotypy score of each rat in the group was taken to compute the median value of the group. Dexfenfluramine (2.5, 5 and 10 mg/kg) or haloperidol (0.5 mg/kg) was injected 1 h before dexamphetamine or apomorphine 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 (18) by placing both front limbs 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, 3, and 4 h after ip injection of dexfenfluramine, haloperidol or distilled water.

#### **Haloperidol and small dose apomorphine induced catalepsy in rats**

Dexfenfluramine (2.5, 5 and 10 mg/kg) was injected 1 h before haloperidol (0.5 and 1 mg/kg) or small doses of apomorphine (0.05 and 0.1 mg/kg). Control groups received 2 ml/kg body weight of distilled water ip 1 h before receiving haloperidol or apomorphine. Animals were evaluated for catalepsy 1 and 2 h after haloperidol or

apomorphine treatment by placing both front limbs 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 non-parametric two tailed Mann-Whitney U-test. The results concerning effects of dexfenfluramine on catalepsy induced by haloperidol and small doses of apomorphine were analysed by the two-tailed Student's unpaired t-test. A P value less than 0.05 was considered as statistically significant.

## RESULTS

5-HT induces lateral head weaving, reciprocal forepaw treading, hind limb abduction, straub tail, tremors, head and body shakes in rats by stimulating the central 5-H<sub>1</sub> and 5-HT<sub>2</sub> receptors (19). In preliminary experiments it was observed that dexfenfluramine at 2.5 mg/kg ip dose did not induce any of the 5-HT mediated behaviours. This indicates that at 2.5 mg/kg ip dose dexfenfluramine does not release 5-HT. At 5 and 10 mg/kg ip doses dexfenfluramine induced dose-dependent degree of head and body shakes and straub tail in 100% of the animals tested (n = 10 for each dose). Further, few rats receiving

10 mg/kg ip dose of dexfenfluramine also sporadically exhibited the other 5-HT mediated behaviours. The behaviours usually manifested by 10 min after drug administration and wore off by 1 h. At 15 mg/kg ip dose dexfenfluramine induced all the 5-HT mediated behaviours in each rat (n = 10), the intensity and frequency of occurrence of these behaviours was higher as compared to the group receiving 10 mg/kg ip dose and the behaviours lasted for about 2 h. The long lasting strong behavioural syndrome induced by 15 mg/kg ip dose of dexfenfluramine in every rat could have non-specifically interfered with the expression of SB induced by the DA agonists and the catalepsy induced by haloperidol and small doses of apomorphine. For subsequent studies dexfenfluramine was therefore used in doses of 2.5, 5 and 10 mg/kg ip and was administered 1 h before the DA agonists, haloperidol and small doses of apomorphine. Further, in the preliminary experiments dexfenfluramine per se at 2.5 to 15 mg/kg ip did not induce SB of the OMV in rats throughout the observation period of 4 h whereas dexamphetamine (5 and 10 mg/kg ip) and apomorphine (1.5 and 3 mg/kg ip) induced dose-dependent SB. The dexamphetamine induced SB, depending on the dose used, manifested about 10 to 20 min after the injection and lasted for about 2 to 2.5 h while the apomorphine induced SB had a rapid onset, within 10 min of injection, and lasted for about 40 to 60 min.

### 1. Effect on DA agonist induced SB in rats

Table I shows the effect of pretreatment with dexfenfluramine and haloperidol on dexamphetamine and apomorphine induced

TABLE I: Effect of dexfenfluramine (DEX) and haloperidol (HAL) pretreatment on dexamphetamine (DAM) and apomorphine (APO) induced stereotyped behaviour in rats.

Study	Group (n=10)	Treatment (mg/kg, ip)	Median SB Score (with ranges)
I.	A.	1. DW+DAM (5)	19.5 (18-22)
		2. DEX (2.5)+DAM (5)	18.5 (17-21)
		3. DEX (5)+DAM (5)	16.0 (14-18)*
		4. DEX (10)+DAM (5)	11.5 (10-14)**
	B.	1. DW+DAM (10)	35.5 (33-37)
		2. DEX (2.5)+DAM (10)	34.5 (32-36)
		3. DEX (5)+DAM (10)	32.0 (29-33)*
		4. DEX (10)+DAM (10)	27.5 (25-29)**
II. A.	1. DW+DAM (5)	19.0 (17-22)	
	2. HAL (0.5)+DAM (5)	0.0	
	B.	1. DW+DAM (10)	35.0 (34-36)
		2. HAL (0.5)+DAM (10)	13.5 (12-14)**
III.	A.	1. DW+APO (1.5)	9.5 (9-11)
		2. DEX (2.5)+APO (1.5)	9.5 (8-12)
		3. DEX (5)+APO (1.5)	10.0 (9-11)
		4. DEX (10)+APO (1.5)	9.0 (8-12)
	B.	1. DW+APO (3)	16.5 (16-18)
		2. DEX (2.5)+APO(3)	16.0 (15-19)
		3. DEX (5)+APO (3)	17.0 (16-18)
		4. DEX (10)+APO (3)	16.5 (15-18)
IV. A.	1. DW+APO (1.5)	10.0 (8-11)	
	2. HAL (0.5)+APO (1.5)	0.0	
	B.	1. DW+APO (3)	16.0 (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 dexamphetamine group by Mann-Whitney's U-test.

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

SB in rats. Pretreatment with 2.5 mg/kg dexfenfluramine did not cause a significant decrease (18.5 vs 19.5, P>0.05) whereas pretreatment with 5 and 10 mg/kg dexfenfluramine caused a significant decrease in the median SB score as compared to their distilled water pretreated control 5 mg/kg dexamphetamine group (16 and 11.5 respectively vs 19.5, P<0.01

and P<0.001 respectively, Study IA). Similarly, pretreatment with 2.5 mg/kg dexfenfluramine did not cause a significant decrease (34.5 vs 35.5, P>0.05) whereas pretreatment with 5 and 10 mg/kg dexfenfluramine caused a significant decrease in the median SB score as compared to their distilled water pretreated control 10 mg/kg dexamphetamine group (32 and 27.5 respectively vs 35.5, P<0.01 and P<0.001 respectively, Study I B).

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 19 of its distilled water pretreated control 5 mg/kg dexamphetamine group (Study II A). 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 (13.5 vs 35, P<0.001, Study IIB).

Pretreatment with 2.5, 5 and 10 mg/kg dexfenfluramine did not significantly influence apomorphine (1.5 and 3 mg/kg) induced SB. The median SB scores of the groups pretreated with 2.5, 5 and 10 mg/kg dexfenfluramine did not differ significantly from the median SB score of their distilled water pretreated control 1.5 mg/kg apomorphine group (9.5, 10 and 9 respectively vs 9.5, P>0.05, Study III A) and 3 mg/kg apomorphine group (16, 17, 16.5 respectively vs 16.5, P>0.05, Study III B).

Animals pretreated with 0.5 mg/kg haloperidol did not exhibit SB following

TABLE II: Effect of dexfenfluramine (DEX) pretreatment on catalepsy induced by haloperidol (HAL) and small doses of apomorphine (APO) 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+HAL (0.5)	33.9±1.59	27.8±1.61	
	2.	DEX (2.5)+HAL (0.5)	36.9±1.36	31.0±1.67	
	3.	DEX (5)+HAL (0.5)	39.4±1.46*	33.5±1.77*	
	4.	DEX (10)+HAL (0.5)	44.1±1.84***	37.5±1.46***	
	B.	1.	DW+HAL (1)	57.5±1.90	50.8±2.04
		2.	DEX (2.5)+HAL (1)	60.6±1.87	54.0±2.10
		3.	DEX (5)+HAL (1)	63.1±1.62*	56.5±1.58*
		4.	DEX (10)+HAL (1)	67.7±1.76***	61.0±1.57***
II. A.	1.	DW+APO (0.05)	27.0±1.22	34.5±1.34	
	2.	DEX (2.5)+APO (0.05)	30.5±1.39	37.8±1.48	
	3.	DEX (5)+APO (0.05)	32.2±1.65**	40.0±1.53**	
	4.	DEX (10)+APO (0.05)	37.3±1.81***	44.7±1.75***	
	B.	1.	DW+APO (0.1)	51.4±1.73	59.2±1.71
		2.	DEX (2.5)+APO (0.1)	54.8±1.75	62.7±1.76
		3.	DEX (5)+APO (0.1)	57.0±1.39**	64.8±1.42**
		4.	DEX (10)+APO (0.1)	61.7±1.80***	69.5±1.81***

\*P<0.05, \*\*P<0.02, \*\*\*P<0.001 as compared to the respective distilled water pretreated control haloperidol or apomorphine group, at the respective testing time interval, by Student's unpaired t-test. DW = Distilled water (2 ml/kg, ip).

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 of their respective distilled water pretreated control 1.5 and 3 mg/kg apomorphine groups (Study IV A and B, respectively).

## 2. Induction of catalepsy in rats

Dexfenfluramine (2.5, 5 and 10 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, all animals (n = 10) treated with haloperidol (1 mg/kg) maintained the imposed posture for more than 10 s at each testing time

interval and hence were considered to be cataleptic.

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

Table II shows the effect of pretreatment with dexfenfluramine on catalepsy induced by haloperidol and small doses of apomorphine in rats. Pretreatment with 2.5 mg/kg dexfenfluramine did not cause a significant increase 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 (36.9 ± 1.36 vs 33.9 ± 1.59 at 1 h and 31.0 ± 1.67 vs 27.8 ± 1.61 at 2 h testing time interval, Study I A). However, pretreatment with 5 and 10 mg/kg dexfenfluramine caused

a significant increase 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 ( $39.4 \pm 1.46$  and  $44.1 \pm 1.84$  respectively vs  $33.9 \pm 1.59$  at 1 h,  $P < 0.05$  and  $P < 0.001$  respectively; and  $33.5 \pm 1.77$  and  $37.5 \pm 1.46$  respectively vs  $27.8 \pm 1.61$  at 2 h testing time interval,  $P < 0.05$  and  $P < 0.001$  respectively, Study I A). Similarly, pretreatment with 2.5 mg/kg dexfenfluramine did not cause a significant increase 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 ( $60.6 \pm 1.87$  vs  $57.5 \pm 1.90$  at 1 h and  $54.0 \pm 2.10$  vs  $50.8 \pm 2.04$  at 2 h testing time interval, Study I B). However, pretreatment with 5 and 10 mg/kg dexfenfluramine caused a significant increase 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 ( $63.1 \pm 1.62$  and  $67.7 \pm 1.76$  respectively vs  $57.5 \pm 1.90$  at 1 h,  $P < 0.05$  and  $P < 0.001$  respectively; and  $56.5 \pm 1.58$  and  $61.0 \pm 1.57$  respectively vs  $50.8 \pm 2.04$  at 2 h testing time interval,  $P < 0.05$  and  $P < 0.001$  respectively, Study I B).

Pretreatment with 2.5 mg/kg dexfenfluramine did not cause a significant increase in the 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 ( $30.5 \pm 1.39$  vs  $27.0 \pm 1.22$  at 1 h and  $37.8 \pm 1.48$  vs  $34.5 \pm 1.34$  at 2 h testing time interval, Study IIA). However, pretreatment with 5 and 10 mg/kg dexfenfluramine caused a significant increase 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 ( $32.2 \pm 1.65$  and  $37.3 \pm 1.81$  respectively vs  $27.0 \pm 1.22$  at 1 h,  $P < 0.02$  and  $P < 0.001$  respectively; and  $40.0 \pm 1.53$  and  $44.7 \pm 1.75$  respectively vs  $34.5 \pm 1.34$  at 2 h testing time interval,  $P < 0.02$  and  $P < 0.001$  respectively, Study IIA). Similarly, pretreatment with 2.5 mg/kg dexfenfluramine did not cause a significant increase 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 ( $54.8 \pm 1.75$  vs  $51.4 \pm 1.73$  at 1 h and  $62.7 \pm 1.76$  vs  $59.2 \pm 1.71$  at 2 h testing time interval, Study IIB). However, pretreatment with 5 and 10 mg/kg dexfenfluramine caused a significant increase 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 ( $57.0 \pm 1.39$  and  $61.7 \pm 1.80$  respectively vs  $51.4 \pm 1.73$  at 1 h,  $P < 0.02$  and  $P < 0.001$  respectively; and  $64.8 \pm 1.42$  and  $69.5 \pm 1.81$  respectively vs  $59.2 \pm 1.71$  at 2 h testing time interval,  $P < 0.02$  and  $P < 0.001$  respectively, Study II B).

## DISCUSSION

Haloperidol induces catalepsy and antagonizes apomorphine stereotypy of OMV in rats by blocking the postsynaptic striatal D2 and D1 DA receptors (12, 14). In the present study treatment with 2.5, 5 and 10 mg/kg dexfenfluramine did not induce catalepsy and pretreatment with these doses of dexfenfluramine failed to antagonize apomorphine-induced SB of OMV in rats. This indicates that at 2.5, 5 and 10 mg/kg

doses dexfenfluramine does not exert postsynaptic striatal D2 and D1 DA receptor blocking activity. Our contention that dexfenfluramine does not block postsynaptic striatal D2 DA receptors, concurs with the report of Garattini et al (20) that dexfenfluramine, unlike the neuroleptics, does not bind significantly to the D2 DA receptors in rat striatal membranes in vitro. Further, our observation, that 1 h pretreatment with 5 and 10 mg/kg doses of dexfenfluramine, which release 5-HT and induce 5-HT mediated behaviours, failed to antagonize apomorphine stereotypy, suggests that the released 5-HT does not exert an inhibitory effect at or beyond the postsynaptic striatal D2 and D1 DA receptor sites. Our observation, that pretreatment with 5-HT releasing doses of dexfenfluramine, did not modify apomorphine stereotypy concurs with the observation of Rotrosen et al (21) and Baldessarini et al (22) that the central 5-HT system does not influence apomorphine - induced SB in rats since pretreatment with 1-tryptophan or 5-hydroxytryptophan, precursors of 5-HT, p-chlorophenylalanine, a 5-HT depletor, and methysergide, a 5-HT<sub>2A/2C</sub> receptor antagonist, had no significant effect on apomorphine stereotypy.

In our study 1 h pretreatment with the 5-HT releasing doses (ie 5 and 10 mg/kg) of dexfenfluramine significantly antagonized dexamphetamine - induced SB. Since 1 h pretreatment with 5 and 10 mg/kg dexfenfluramine had failed to antagonize apomorphine stereotypy it indicates that antagonism of dexamphetamine induced SB by dexfenfluramine is most probably not due to any effect of dexfenfluramine or 5-HT at or beyond the postsynaptic

striatal D2 and D1 DA receptor sites. We therefore hypothesise that dexfenfluramine antagonizes dexamphetamine stereotypy by functionally antagonizing DAergic neurotransmission presynaptically ie at the level of cell bodies and nerve terminals of the nigrostriatal DAergic neurons.

Antagonism of dexamphetamine stereotypy by dexfenfluramine pretreatment is explained by us as follows: Biochemical studies have demonstrated that dexfenfluramine, through the released 5-HT, increases the intraneuronal metabolism of DA in the rat striatum (23). Subsequent biochemical and electrophysiological studies have demonstrated that 5-HT inhibits the synthesis and release of DA from rat nigrostriatal DAergic neurons by stimulating the 5-HT<sub>2A/2C</sub> receptors located on the cell bodies and axonal terminals of the nigrostriatal DAergic neurons (2,3). We postulate that dexfenfluramine, through the released 5-HT, decreases the synthesis of DA and increases the intraneuronal metabolism of DA. Consequently the stores of DA in the nigrostriatal DAergic neurons are decreased. As less amount of DA is now available for release by dexamphetamine there is antagonism of dexamphetamine stereotypy in rats.

In the present study pretreatment with the 5-HT releasing doses (ie 5 and 10 mg/kg) of dexfenfluramine potentiated the cataleptic effect of 0.5 and 1 mg/kg haloperidol at both 1 and 2 h testing time intervals. Potentiation of haloperidol catalepsy by 5 and 10 mg/kg doses of dexfenfluramine is explained as follows:

Normally, 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 (16). 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 (16). We hypothesise that dexfenfluramine, through the released 5-HT, decreases the stores of DA in the nigrostriatal DAergic neurons. Thus less amount of DA is available for release during the haloperidol - induced compensatory 'feed - back' increase of nigrostriatal DAergic neuronal activity. As a result the haloperidol - induced blockade of the postsynaptic striatal D2 and D1 DA receptors is counteracted to a lesser extent with resultant potentiation of haloperidol catalepsy.

Pretreatment with 5-HT releasing doses (ie 5 and 10 mg/kg) of dexfenfluramine also potentiated the cataleptic effect of 0.05 and 0.1 mg/kg ip apomorphine at both 1 and 2 h testing time intervals. Potentiation of the catalepsy induced by small doses of apomorphine by dexfenfluramine pretreatment has been explained as follows: The two drugs reduce the stores of DA in the nigrostriatal DAergic neurons by acting through different mechanisms. Dexfenfluramine, through the released 5-HT, inhibits the synthesis of DA and increases the intraneuronal metabolism of DA whereas small doses of apomorphine decrease the synthesis of DA via selective

stimulation of the presynaptic D2 DA autoreceptors. Their consecutive administration therefore produces a greater reduction in the intraneuronal stores of DA as compared to the reduction occurring in distilled water pretreated control groups receiving small doses of apomorphine only. A greater reduction in the intraneuronal stores of DA, along with the inhibitory effect of small doses of apomorphine on DA release, produces a greater degree of functional lack of DA at the postsynaptic striatal D2 and D1 DA receptor sites. This results in potentiation of the catalepsy induced by small doses of apomorphine in rats.

To conclude, our study indicates that dexfenfluramine per se or through the released 5-HT does not exert an inhibitory effect at or beyond the postsynaptic striatal D2 and D1 DA receptor sites. However, pretreatment with 5 and 10 mg/kg ip dexfenfluramine, through the released 5-HT, decreases the synthesis of DA and increases the intraneuronal metabolism of DA. As a result the stores of DA in the nigrostriatal DAergic neurons are decreased. Consequently pretreatment with 5-HT releasing doses of dexfenfluramine (ie 5 and 10 mg/kg ip) antagonize dexamphetamine stereotypy and potentiate catalepsy induced by haloperidol or small doses of apomorphine.

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