ANTAGONISM OF BROMOCRIPTINE-INDUCED CAGE CLIMBING BEHAVIOUR IN MICE BY THE SELECTIVE D-2 DOPAMINE RECEPTOR ANTAGONISTS, METOCLOPRAMIDE AND MOLINDONE

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Summary : Bromocriptine (5-30 *mg/kg*, ip), 2 hr after administration, induced cage climbing behaviour in mice. Pretreatment with haloperidol, an antagonist of both D-1 and D-2 dopamine receptors, metoclopramide and molindone, the selective D-2 dopamine receptor antagonists, effectively antagonised bromocriptine-induced climbing behaviour. The results indicate that bromocriptine most probably induces climbing behaviour in mice by stimulating the postsynaptic striatal D-2 dopamine receptors.

Key words : bromocriptine haloperidol metoclopramide molindone climbing behaviour mice

INTRODUCTION

Apomorphine, the dopamine (DA) agonist, induces cage climbing behaviour in mice by directly stimulating the postsynaptic striatal DA receptors (8). Recent work suggests existence of more than one type of DA receptor in the mammalian brain (1, 5). Kebabian and Calne (5) have classified DA receptors according to the presence (D-1 receptor) or absence of adenylate cyclase linkage (D-2 receptor). While the action of DA is mediated by both of the proposed DA receptors, apomorphine has agonist actions on D-2 receptors but is only a partial agonist at D-1 receptor sites, and the ergot derivatives, bromocriptine and lergotrile, have agonist actions only at the D-2 receptor

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(5, 6). Further, in the adenylate cyclase model, chlorpromazine and haloperidol have antagonistic actions on both receptor types while metoclopramide, sulpiride and molindone are selective D-2 receptor antagonists (4, 5).

Recently, Gianutsos and Palmeri (3) have reported that, of the three ergot derivatives which they studied, only pergolide and bromocriptine induced climbing behaviour in mice while lergotrile failed to do so. Since lergotrile (a D-2 DA receptor agonist, 5) did not induce climbing and pergolide (which stimulates the DA-sensitive adenylate cyclase, 11) and bromocriptine (which does not stimulate DA sensitive adenylate cyclase *in vitro* but stimulates it and increases the striatal cyclic AMP levels *in vivo*, 5, 10) induced climbing, it was suggested (3) that stimulation of striatal D-1 DA receptors might be necessary for climbing to be produced. To elucidate whether D-1 or D-2 DA receptor activation by bromocriptine is responsible for the production of climbing behaviour we have studied the effect of pretreatment with haloperidol, an antagonist of both D-1 and D-2 DA receptors, metoclopramide and molindone, selective D-2 DA receptor antagonists, on bromocriptine-induced cage climbing behaviour in mice.

MATERIAL AND METHODS

Male albino mice, 20 to 30 *g*, in groups of 10 for each treatment and allowed free access to a standard diet and tap water were used. Each animal was used once only. All observations were made between 10.00 and 16.00 hr at 25 to 27°C in a noiseless, diffusely illuminated room. During the experiments the animals were placed in individual wire cages (27 *cm* × 20 *cm* and 15 *cm* high), 30 min before drug treatment to allow adaptation. Observations were made blind with respect to the treatments used. The effect of haloperidol, metoclopramide and molindone pretreatment on bromocriptine-induced cage climbing behaviour was studied by the method of Costall *et al.* (2). The intensity of climbing behaviour induced by bromocriptine was assessed over a 60 min observation period, 3 hr after injection of bromocriptine. The animals were tested individually for climbing behaviour taking 'the percentage of time spent climbing during the 60 min period' as a measure of climbing ('climbing index'). Further, the maximum time (in min) spent in a single climb throughout the 60 min observation period was also recorded.

The drugs used were bromocriptine (Sandoz), molindone HCl (Endo), metoclopramide monohydrochloride ('Reglan' injection, Cosme Farma) and haloperidol ('Serenace' injection, Searle). Bromocriptine was dissolved in minimum volume of

1 N HCl, diluted with distilled water and neutralised to pH 5.6 with $NaHCO_3$. Molindone was dissolved in distilled water while metoclopramide and haloperidol injection solutions were diluted to required strength with distilled water. All drug solutions were prepared immediately before use and were injected ip in a volume of 0.1 *ml*/10 *g* body weight. Doses refer to the forms mentioned. Molindone, metoclopramide and haloperidol (or vehicle, in control groups) were injected 20 min before bromocriptine.

All tests for statistical significance were performed by a two-tailed Student's t-test ($P<0.05$).

RESULTS

In preliminary experiments the time-course and dose-dependent nature of bromocriptine-induced climbing behaviour was ascertained by observing the animals over a period of 5 hr after injection of bromocriptine (5-30 *mg*/*kg*). Bromocriptine (5-30 *mg*/*kg*) produced a time-dependent biphasic action on motor behaviour. During the first 2 hr after injection, bromocriptine (5-30 *mg*/*kg*) depressed the locomotor and exploratory activity of the animals. The animals remained quiet but were alert and responsive to sensory stimuli. After this initial 2 hr delay, bromocriptine (5-30 *mg*/*kg*) caused stimulation of locomotor activity accompanied by climbing behaviour which persisted throughout the remaining 3 hr period. Bromocriptine at 5 *mg*/*kg* induced climbing behaviour in 40% (n=10) of the animals, while at 10, 20 and 30 *mg*/*kg* it induced climbing behaviour in 100% (n=10) of the animals tested. Maximum intensity of climbing behaviour was observed during the 3 to 4 hr time interval after injection of bromocriptine. Since bromocriptine, 10, 20 and 30 *mg*/*kg* induced a threshold to submaximal response respectively, higher doses were not tested and these doses were used for subsequent interaction studies. Vehicle treated control animals (n=10) were also observed for a period of 5 hr after injection. Except for brief spells of locomotor, exploratory and grooming activities, these animals remained quiet for major portion of the time and did not exhibit climbing behaviour.

Pretreatment with haloperidol (0.25 *mg*/*kg*), metoclopramide (5 *mg*/*kg*) and molindone (2.5 *mg*/*kg*) abolished the climbing behaviour induced by 10 *mg*/*kg* bromocriptine and significantly decreased the intensity of climbing behaviour induced by 20 and 30 *mg*/*kg* bromocriptine (Table I). Pretreatment with haloperidol (0.5 *mg*/*kg*), metoclopramide (10 *mg*/*kg*) and molindone (5 *mg*/*kg*) abolished the climbing behaviour induced by 20 *mg*/*kg* bromocriptine and significantly decreased the intensity of climbing behaviour induced by 30 *mg*/*kg* bromocriptine (Table I). Climbing behaviour induced by

30 *mg/kg* bromocriptine was abolished by pretreatment with 1 *mg/kg* haloperidol, 20 *mg/kg* metoclopramide and 10 *mg/kg* molindone (Table I).

TABLE I : Effect of haloperidol (HAL), metoclopramide (MET) and molindone (MOL) pretreatment on bromocriptine (BRO)-induced cage climbing behaviour in mice.

	Treatment (dose mg/kg)	*Climbing index (%) Mean±S.E.M.*	*Maximum time (min) Mean±S.E.M.*
	Vehicle	0.0	0.0
1.	BRO 10	36.7±3.2	5.5±0.6
2.	HAL 0.25 + BRO 10	0.0	0.0
3.	BRO 10	35.9±2.7	5.2±0.4
4.	MET 5 + BRO 10	0.0	0.0
5.	BRO 10	36.4±2.9	5.4±0.9
6.	MOL 2.5 + BRO 10	0.0	0.0
1.	BRO 20	65.7±3.4	10.9±0.7
2.	HAL 0.25 + BRO 20	26.9±2.5*	3.2±0.5*
3.	HAL 0.5 + BRO 20	0.0	0.0
4.	BRO 20	64.9±2.8	10.5±0.8
5.	MET 5 + BRO 20	27.2±2.6*	3.4±0.6*
6.	MET 10 + BRO 20	0.0	0.0
7.	BRO 20	65.4±3.2	10.7±0.5
8.	MOL 2.5 + BRO 20	26.7±2.9*	3.6±0.4*
9.	MOL 5 + BRO 20	0.0	0.0
1.	BRO 30	85.9±3.5	15.7±0.9
2.	HAL 0.25 + BRO 30	49.2±3.3*	7.2±0.4*
3.	HAL 0.5 + BRO 30	22.7±2.7*	2.4±0.6*
4.	HAL 1 + BRO 30	0.0	0.0
5.	BRO 30	86.2±3.6	15.9±0.7
6.	MET 5 + BRO 30	50.1±3.4*	7.5±0.5*
7.	MET 10 + BRO 30	24.9±2.9*	2.7±1.1*
8.	MET 20 + BRO 30	0.0	0.0
9.	BRO 30	85.5±3.7	15.4±0.7
10.	MOL 2.5 + BRO 30	49.5±3.5*	7.3±0.6*
11.	MOL 5 + BRO 30	23.7±2.8*	2.5±0.4*
12.	MOL 10 + BRO 30	0.0	0.0

*$P<0.01$ or less. Numerals following drugs indicate their doses (*mg/kg*).

DISCUSSION

Our observations, that bromocriptine (5-30 *mg/kg*), 2 hr after injection, induces cage climbing behaviour in mice and that the bromocriptine-induced climbing behaviour is antagonised by haloperidol pretreatment, concur with those of Gianutsos and Palmeri (3). However, our observation that pretreatment with metoclopramide and molindone, the selective D-2 DA receptor antagonists (5), also antagonised bromocriptine-induced climbing behaviour indicates that bromocriptine induces climbing behaviour by stimulating the postsynaptic striatal D-2 DA receptors and contradicts the suggestion of Gianutsos and Palmeri (3) that stimulation of D-1 (adenylate cyclase-linked) DA receptors by DA agonists is essential for climbing to be produced. In this connection we would like to emphasize that though bromocriptine (given ip) increases striatal cyclic AMP concentrations by stimulating the striatal DA-sensitive adenylate cyclase i.e. D-1 DA receptors, maximum increase of striatal cyclic AMP concentrations occur about 10 min after the injection of the drug, and the content of cyclic AMP returns to control values within 1 hr (10). Thus the short-lived increase in striatal cyclic AMP concentration occurs at a time when locomotor function is not enhanced by the drug and does not correspond with the drug-induced stimulation of locomotor activity and occurence of climbing behaviour. Our contention that stimulation of postsynaptic striatal D-2 DA receptors by DA agonists might be mainly responsible for the production of climbing behaviour is supported by the observation that tha climbing behaviour induced by apomorphine, which has agonist actions on D-2 DA receptors but is a partial agonist at D-1 DA receptor sites (6), was also antagonised by metoclopramide, sulpiride (2) and molindone (7), the selective D-2 DA receptor antagonists. Further, our results are also in agreement with the generally accepted view that the D-2 DA receptor mediates the postsynaptic behavioural effects of DA in the brain, since potencies of various DA agonists at this site correlates with their potencies in alleviating Parkinson's disease and in eliciting rotational and stereotyped behaviours (9).

In conclusion, on the basis of our results, we suggest that bromocriptine induces climbing behaviour in mice by stimulating the postsynaptic striatal D-2 DA receptors.

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