

EFFECT OF DRUGS INFLUENCING CENTRAL 5-HYDROXYTRYPTAMINE MECHANISMS ON AMANTADINE-INDUCED STEREOTYPED BEHAVIOUR IN THE RAT

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Summary : Pretreatment with L-tryptophan, a precursor of 5-HT, was found to decrease the intensity of stereotyped behaviour induced by amantadine, while methysergide, a 5-HT antagonist, was found to increase the intensity of amantadine-induced stereotypy. These results suggest that the intensity of amantadine-induced stereotypy depends on the balance between central dopamine and 5-HT systems and that the central 5-HT systems may have an opposing, tonic effect upon central dopamine systems involved in the mediation of stereotypy. In contrast to L-tryptophan, however, pretreatment with quipazine, a 5-HT agonist, and clomipramine, a selective 5-HT neuronal reuptake blocker, was found to potentiate the stereotyped behaviour induced by amantadine.

Key words : amantadine
methysergide

L-tryptophan
stereotyped behaviour

clomipramine
quipazine

INTRODUCTION

The intensity of the stereotyped behaviour (SB) induced by the indirectly acting (amphetamines) and directly acting dopamine (DA) agonists (apomorphine) is influenced by drugs affecting the central 5-hydroxytryptamine (5-HT) systems (3, 18, 19). Pretreatment with methysergide, a 5-HT receptor antagonist, and p-chlorophenylalanine, a specific depletor of brain 5-HT, potentiated amphetamine and apomorphine-induced SB, while pretreatment with 5-HT precursors, 5-hydroxytryptophan and L-tryptophan, antagonized it (3, 9, 11, 18, 19). These results suggest that the central 5-HT systems may have an opposing tonic effect upon the central DA systems involved in the mediation of SB.

Amantadine, an antiparkinson drug, which acts as a DA agonist mainly by releasing DA from the DA neurones and to some extent by directly stimulating the post-synaptic

DA receptors, is reported to induce SB in rats (2). In the present study we have investigated the effects of pretreatment with L-tryptophan, clomipramine, quipazine, and methysergide on amantadine-induced SB in the rat. L-tryptophan, a precursor of 5-HT, was administered systemically to increase brain 5-HT levels (1). Clomipramine, an iminodibenzyl tricyclic antidepressant drug, is reported to be a more effective and selective blocker of neuronal uptake of 5-HT (16). Quipazine is reported to specifically stimulate post-synaptic 5-HT receptors (15) and also to stimulate the release (8) and inhibit the reuptake of 5-HT (10). Methysergide was used as a 5-HT receptor antagonist.

MATERIAL AND METHODS

Male albino rats, 120 to 180 g, in groups of ten 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 27 to 30°C in a noiseless, diffusely illuminated room.

The drugs used were: amantadine hydrochloride (Ciba-Geigy), L-tryptophan (Sigma), clomipramine hydrochloride (Ciba-Geigy), quipazine maleate (Miles Laboratories) and methysergide hydrogen maleinate (Sandoz). All drugs were dissolved in distilled water except L-tryptophan which was dissolved in a minimum quantity of HCl and made up to volume with distilled water. All drugs were injected ip in a volume of 0.2 ml/100 g body weight, except methysergide and L-tryptophan which were administered in a volume of 0.5 ml/100 g body weight. All doses refer to the salt except for L-tryptophan. Control groups received the requisite volume of vehicle ip before receiving amantadine.

The effect of drug pretreatment on the SB induced by 100 mg/kg (maximum tolerated dose) amantadine was studied by the method of Costall *et al.* (4). For observation the animals were placed in individual cages made of wire netting, measuring 30 cm x 20 cm and 20 cm high. They were placed in the observation cages 30 min before drug treatment to allow adaptation to the environment. The intensity of SB was assessed over a 30 sec observation period at 10 min intervals for 3 hr according to the following scoring system: 0: short lasting period of locomotor activity but no SB; 1: discontinuous sniffing, constant exploratory activity; 2: continuous sniffing and small head movements, periodic exploratory activity; 3: continuous sniffing and small head movements, discontinuous gnawing, biting or licking and very brief periods of locomotor activity and 4: continuous gnawing, biting or licking, no exploratory activity and occasional backward locomotion.

The statistical significance of differences between means was calculated by the Student's unpaired t-test. The level of significance chosen was $P < 0.05$.

RESULTS

Amantadine at 25 mg/kg induced no SB, while at doses of 50 and 75 mg/kg, it induced SB of score 1 intensity in 40% (n=10) and 100% (n=10) of the animals, respectively. At 100 mg/kg dose amantadine induced SB of score 2 intensity in 100% (n=40) of the animals tested. Doses beyond 100 mg/kg produced convulsions and death.

1. Effect of L-tryptophan on amantadine-induced SB in rats :

L-tryptophan (100 and 200 mg/kg) treated rats did not exhibit any obvious behavioural syndrome and appeared like the vehicle treated animals. Pretreatment with 100 mg/kg of L-tryptophan significantly decreased while pretreatment with 200 mg/kg of L-tryptophan completely abolished the SB induced by 100 mg/kg of amantadine (Table I).

TABLE I : Effect of pretreatment with L-tryptophan (TRYP), clomipramine (CIMI), quipazine (QUIP) and methysergide (METH) on amantadine (AMAN)-induced stereotyped behaviour in rats.

Treatment (dose mg/kg)	Pretreatment period (min)	Intensity score Mean \pm S.E.M.
1. AMAN 100		2.0 \pm 0.00
2. TRYP 100+AMAN 100	60	1.1 \pm 0.10***
3. TRYP 200+AMAN 100	60	0
1. AMAN 100		2.0 \pm 0.00
2. CIMI 5+AMAN 100	30	2.3 \pm 0.15
3. CIMI 10+AMAN 100	30	2.6 \pm 0.16*
4. CIMI 20+AMAN 100	30	2.9 \pm 0.10***
1. AMAN 100		2.0 \pm 0.00
2. QUIP 0.5+AMAN 100	60	2.4 \pm 0.16
3. QUIP 1+AMAN 100	60	2.7 \pm 0.15**
4. QUIP 2+AMAN 100	60	3.0 \pm 0.00***
1. AMAN 100		2.0 \pm 0.00
2. METH 2.5+AMAN 100	30	2.2 \pm 0.13
3. METH 5+AMAN 100	30	2.6 \pm 0.16*
4. METH 10+AMAN 100	30	2.9 \pm 0.10***

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Numerals following the drugs indicate their doses (mg/kg).

2. *Effect of clomipramine pretreatment on amantadine-induced SB in rats :*

Clomipramine (5, 10 and 20 *mg/kg*) treated rats did not exhibit any obvious behavioural syndrome and appeared like the vehicle-treated animals. Pretreatment with 5 *mg/kg* of clomipramine did not significantly affect the amantadine-induced SB (Table I). However, pretreatment with 10 and 20 *mg/kg* of clomipramine did significantly increase the intensity of SB induced by 100 *mg/kg* of amantadine (Table I).

3. *Effect of quipazine pretreatment on amantadine-induced SB in rats :*

Quipazine (0.5, 1 and 2 *mg/kg*) itself induced an increase in locomotor activity, slight tremor, sniffing, and rubbing of the nose. This lasted for 30-40 min after injection of quipazine. Pretreatment with 0.5 *mg/kg* of quipazine did not significantly affect the amantadine-induced SB (Table I). However, pretreatment with 1 and 2 *mg/kg* of quipazine did significantly increase the intensity of SB induced by 100 *mg/kg* of amantadine (Table I).

4. *Effect of methysergide pretreatment on amantadine-induced SB in rats :*

Methysergide (2.5, 5 and 10 *mg/kg*) alone had no effect upon behavior. Pretreatment with 2.5 *mg/kg* of methysergide did not significantly affect the amantadine-induced SB (Table I). However, pretreatment with 5 and 10 *mg/kg* of methysergide did significantly increase the intensity of SB induced by 100 *mg/kg* of amantadine (Table I).

DISCUSSION

Amantadine induced only low intensity SB characterized by sniffing. Even after its dose was increased to the maximum tolerated one of 100 *mg/kg*, it produced SB not exceeding rating 2. These findings concur with the observation of other workers (2,5).

In the present experiments drugs which influence the central 5-HT mechanisms have been found to affect the SB induced by amantadine. L-tryptophan, a precursor of 5-HT, which is reported to decrease the intensity of methamphetamine stereotypy (3), was also found to decrease the intensity of SB induced by amantadine while methysergide, a 5-HT receptor antagonist, which is reported to potentiate amphetamine and apomorphine-induced SB (3, 18, 19), was also found to increase the intensity of amantadine-induced SB. Our findings with L-tryptophan and methysergide suggest that, as is the case with the SB induced by other DA agonists, the intensity of amantadine-induced

SB also depends on the balance between central DA and 5-HT systems and that the central 5-HT system may be exerting an opposing tonic effect upon the central DA systems involved in the mediation of SB.

The results of our experiments with quipazine and clomipramine pretreatment, however, differ from those with L-tryptophan pretreatment. In contrast to L-tryptophan, pretreatment with quipazine and clomipramine was found to increase the intensity of amantadine-induced SB. The reasons for this discrepancy can only be speculated at this time. Quipazine and clomipramine, in addition to blocking the uptake of 5-HT, have also been reported to block the uptake of DA (7, 10, 14). Further, quipazine has been reported to inhibit the monoamine oxidase (MAO) enzyme (6), while clomipramine, like imipramine, might possess an inhibitory action on MAO type B enzyme (17) for which DA is one of the naturally occurring substrates (20). These additional actions of quipazine and clomipramine may be responsible for increasing the intensity of amantadine-induced SB. Further, quipazine and clomipramine have been reported to potentiate both methamphetamine and apomorphine-induced SB (3,12,13).

In conclusion, on the basis of our results with L-tryptophan and methysergide, we would like to suggest that the intensity of amantadine-induced SB depends on the balance between central DA and 5-HT systems, and that the central 5-HT systems may have an opposing tonic effect upon central DA systems involved in the mediation of SB.

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