SHORT COMMUNICATION

EFFECT OF α-METHYL-P-TYROSINE ON NEUROLEPTIC-INDUCED CATALEPSY IN RAT

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Summary : Pretreatment with α-methyl-p-tyrosine, a tyrosine hydroxylase inhibitor, was found to increase the intensity of catalepsy induced by haloperidol, chlorpromazine and molindone. The drug probably decreases the synthesis of dopamine and makes less dopamine available for release and to compete with the neuroleptic for the postsynaptic striatal dopamine receptor sites with resultant potentiation of the neuroleptic-induced catalepsy.

Key words : α-methyl-p-tyrosine, haloperidol, chlorpromazine, catalepsy, rat, molindone

INTRODUCTION

Neuroleptics like haloperidol, chlorpromazine and molindone, induce catalepsy in animals, and some extrapyramidal side effects in man by blocking postsynaptic striatal dopamine (DA) receptors (5, 8). Recently, pretreatment with α-methyl-p-tyrosine, a drug which specifically depletes brain catecholamines by inhibiting the tyrosine hydroxylase (10), was reported to potentiate haloperidol-induced blockade of conditioned avoidance response (9) and the suppressant effect of neuroleptics on operant (1, 2) and tail-pinch induced eating behaviour (4). Further, in clinical studies, treatment with α-methyl-p-tyrosine not only potentiated the antischizophrenic action of neuroleptics (6, 12) but at the same time also aggravated their extrapyramidal side effects (11). Since neuroleptic-induced catalepsy in animals is analogous to neuroleptic-induced parkinsonism in man (8), we have investigated the effect of pretreatment with α-methyl-p-tyrosine on catalepsy induced by three different neuroleptic agents, viz., haloperidol, chlorpromazine and molindone.

MATERIAL AND METHODS

Male albino rats, 150 to 200 *g*, were allowed free access to a standard diet and tap water and were used in groups of 10. 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.

For assessment of catalepsy, the rats were placed individually in Perspex cages (30 x 20 x 20 cm) 30 min before drug treatments to allow for adaptation. Catalepsy was evaluated by placing both front limbs of the animal over an 8 cm high horizontal bar and measuring the time that the animal maintained this posture. Scoring, modified from that of Costall and Naylor (7), was as follows : maintaining the cataleptic posture for 0 to 10 sec, 0; for 10 to 30 sec, 1; for 30 to 60 sec, 2; for 1 to 2 min, 3; and for 2 min and more, 4. Animals were tested for catalepsy 0.5, 1.0, and 2.0 hr after neuroleptic treatment.

The drugs used were : dl-α-methyl-p-tyrosine methyl ester HCl (Sigma), haloperidol (Serenace injection, Searle), chlorpromazine HCl (May and Baker) and molindone HCl (Endo). All drugs were used as aqueous solutions, and were injected ip in a volume of 0.2 *ml*//100 *g* body weight. Doses refer to the forms mentioned. α-Methyl-p-tyrosine (or distilled water, in control groups) was injectecd 2 hr before haloperidol, chlorpromazine or molindone.

Statistical significance of differences between groups was tested by a two-tailed Mann-Whitney U-test for non-parametric data.

RESULTS

α-Methyl-p-tyrosine (50 and 100 *mg/kg*) did not produce any apparent change in the muscle tone or any detectable changes in the gross behaviour of the animals nor did it induce catalepsy when the rats were tested upto 5 hr after injection.

Haloperidol (0.5 and 1 *mg/kg*), chlorpromazine (7.5 and 10 *mg/kg*) and molindone (2.5 and 5 *mg/kg*) induced a state of mild sedation and a dose-dependent degree of catalepsy (Table I), without loss of righting reflex or apparent change in muscle tone or motor coordination. The cataleptic effect was present at 30 min and reached maximum 1 hr after the injection (Table I).

Pretreatment with α-methyl-p-tyrosine (50 and 100 *mg/kg*) significantly increased the intensity of catalepsy induced by haloperidol (0.5 and 1 *mg/kg*), chlorpromazine (7.5 and 10 *mg/kg*) and molindone (2.5 and 5 *mg/kg*), at all the observation sessions (Table I).

TABLE I : Effect of pretreatment with α-methyl-p-tyrosine (AMT), given 2 hr before, on the intencity of catalepsy induced by haloperidol (HAL), chlorpromazine (CPZ) and molindone (MOL) in rats.

Pretreatment and neuroleptic (dose, mg/kg)	*Catalepsy Score (Mean±S.E.M.)*		
	0.5 hr	1.0 hr	2.0 hr
1. Vehicle (water)+HAL 0.5	0.8±0.13	1.2±0.13	1.1±0.10
2. AMT 50+HAL 0.5	1.5±0.16*	2.0±0.00*	1.9±0.10*
3. AMT 100+HAL 0.5	1.9±0.10*	2.3±0.15*	2.1±0.10*
1. Vehicle (water)+HAL 1	1.8±0.13	2.3±0.15	2.2±0.13
2. AMT 50+HAL 1	2.6±0.16*	3.1±0.10*	2.9±0.10*
3. AMT 100+HAL 1	2.8±0.13*	3.5±0.16*	3.3±0.15*
1. Vehicle (water)+CPZ 7.5	0.7±0.15	1.1±0.10	1.0±0.00
2. AMT 50+CPZ 7.5	1.4±0.16*	2.0±0.00*	1.9±0.10*
3. AMT 100+CPZ 7.5	1.7±0.15*	2.2±0.13*	2.0±0.00*
1. Vehicle (water)+CPZ 10	1.8±0.13	2.2±0.13	2.1±0.10
2. AMT 50+CPZ 10	2.5±0.16*	3.0±0.00*	2.9±0.10*
3. AMT 100+CPZ 10	2.9±0.10*	3.3±0.15*	3.2±0.13*
1. Vehicle (water)+MOL 2.5	0.6±0.16	1.1±0.10	1.0±0.00
2. AMT 50+MOL 2.5	1.3±0.15*	1.9±0.10*	1.8±0.13*
3. AMT 100+MOL 2.5	1.6±0.16*	2.2±0.13*	2.0±0.00*
1. Vehicle (water)+MOL 5	1.5±0.16	2.0±0.00	1.9±0.10
2. AMT 50+MOL 5	2.2±0.13*	2.9±0.10*	2.7±0.15*
3. AMT 100+MOL 5	2.6±0.16*	3.2±0.13*	3.1±0.10*

*$P<0.05$ (or less) in comparison with respective control group.

DISCUSSION

Our observation that α-methyl-p-tyrosine increases the intensity of neuroleptic-induced catalepsy is in agreement with the reports that the agent potentiates haloperidol-induced blockade of conditioned avoidance response (9), the suppressant effect of neuroleptics on operant (1, 2) and tail-pinch induced eating behaviour (4), and that it aggravates the extrapyramidal side effects of neuroleptics (11).

Ahlenius and Engel (1, 2) and Antelman *et al.* (4) have explained the α-methyl-p-tyrosine-induced potentiation of the suppressant effect of neuroleptics on operant and

tail-pinch induced eating behaviour as follows. Normally, following the blockade of the postsynaptic DA receptors by neuroleptics, there is a compensatory 'feed-back' increase of DA neuronal activity with resultant increase in DA release which counteracts to some extent the neuroleptic-induced blockade of DA receptors (3). The increase in DA release is accompanied by an increase in tyrosine hydroxylase activity and DA synthesis (13). The authors have postulated that α-methyl-p-tyrosine by inhibiting tyrosine hydroxylase decreases the synthesis of DA and makes less DA available for release and to compete with the neuroleptic for the postsynaptic DA receptor sites with resultant potentiation of the suppressant effect of neuroleptics on operant and tail-pinch induced eating behaviour. The enhancement of neuroleptic-induced catalepsy by α-methyl-p-tyrosine may have a similar explanation.

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