Further evidence in support of a common adrenergic mechanism for the facilitatory action on learning of amphetamine and nicotine in rats

Pretreatment with α-methyl-*p*-tyrosine (α-MT), at doses that themselves had no effect, markedly depressed the facilitatory action of amphetamine and nicotine on learning, as well as the capacity to acquire a conditioned response (CR) in rats submitted to cold. The administration of dopa produced a partial recovery of these depressant effects, which pointed out to the participation of catecholamines in the learning process and suggested a common adrenergic mechanism for the action of amphetamine and nicotine (Orsingher & Fulginiti, 1971).

Since MAO inhibitors partially prevent the catecholamine depletion and the behavioral depression induced by α-MT (Neff & Costa, 1966; Moore & Rech, 1967; Dominic & Moore, 1969) and antagonize the anti-amphetamine effects of α-MT (Weissman & Koe, 1965; Weissman, Koe & Tenen, 1966), we decided to test the action of a pretreatment with MAO inhibitors on the effects shown by the interaction of α-MT with amphetamine, nicotine or cold on learning.

Adult albino rats of either sex, 180–250 g, were trained for acquisition of a CR in a shuttle-box, using a modified Warner-cage (Bovet, Gatti & Franck, 1961). Animals were presented with 60 trials, at 30s inter-trial intervals. Each trial consisted of a sound of a buzzer (conditioned stimulus), which, after 5 s from its onset, overlapped with electric shocks (50 V, 50 Hz) delivered to a floor grid. Occurrence of a barrier-crossing response resulted in interruption of all stimulation; response to the buzzer alone, i.e., in the first 5 s of stimulation, was considered a CR. Results were expressed as percentage of CR for each session of 60 trials. Nialamide (30 mg kg^{-1}) and α-MT (30 mg kg^{-1}) were injected 19 and 3 h before training, respectively. (±)-Amphetamine sulphate and nicotine (2 and 0·2 mg kg^{-1}) were injected 10 min before trials.

Table 1 shows that pretreatment with nialamide induced a significant increase in the number of CRs as compared with the saline control group, and prevented the depressant effect observed by the interaction of α-MT with amphetamine and nicotine. In another experiment, nialamide (30 + 30 mg kg^{-1}, 19 and 5 h before training) was given to rats that received α-MT (30 mg kg^{-1}) 3 h before trials and were then kept in a cold environment (4–6°) until the start of the training routine. Nialamide produced a significant increase in the number of CRs in animals exposed to cold, and thus counteracted the depressant effect seen after the association of α-MT with cold (Table 2).

Table 1. *Effect of nialamide on the interaction of α-MT with amphetamine and nicotine on the acquisition of a conditioned response (CR).*

Group	Treatment	Dose mg kg^{-1}	% CR ± s.e.	*P*
1	Saline	—	55·4±6·6 (12)	
2	Nialamide	30	72·2±1·0 (10)	1 *vs* 2: <0·05
3	Amphetamine	2	77·3±3·5 (10)	1 *vs* 3: <0·02
4	α-MT+amphetamine	30+2	4·7±2·8 (6)	3 *vs* 4: <0·001
5	Nialamide+α-MT+amphetamine	30+30+2	74·2±5·8 (7)	3 *vs* 5: N.S.
6	Nicotine	0·2	72·3±3·8 (11)	1 *vs* 6: <0·05
7	α-MT+nicotine	30+0·2	4·8±1·8 (9)	6 *vs* 7: <0·001
8	Nialamide+α-MT+nicotine	30+30+0·2	65·5±5·0 (7)	6 *vs* 8: N.S.

Significance of differences were calculated by a Student's *t*-test.
Number of animals in each group in brackets.

Table 2. *Effect of nialamide on interaction of α-MT and cold on the acquisition of a CR.*

Group	Treatment	Dose mg kg^{-1}	%CR ± s.e.	*P*
1	Saline (room temperature)	—	44·2±8·8 (8)	
2	Saline+cold	—	35·4±5·4 (10)	1 *vs* 2: N.S.
3	Nialamide +cold	30+30	69·5±3·8 (8)	2 *vs* 3: <0·001
4	α-MT+cold	30	8·3±3·8 (13)	2 *vs* 4: <0·001
5	Nialamide+α-MT+cold	30+30+30	46·7±5·0 (10)	2 *vs* 5: N.S.

No inter-trial crossing (i.e., unmotivated responses), that may be considered as a sign of increased motor activity, was observed in animals treated with nialamide.

Amphetamine (Fulginiti & Orsingher, 1971), nicotine (Bhagat, Kramer & Seifter, 1967; Bhagat, 1970) and exposure to cold (Gordon, Spector & others, 1966) produce release of brain catecholamines. Since α-MT, at the doses used reduces the level of brain catecholamines to 56% of normal, we suggested that the depressant effect of amphetamine, nicotine or cold after tyrosine-hydroxylase inhibition by α-MT might be due to depletion of "functional pools" of catecholamines, rather than to the degree of total catecholamine depletion (Orsingher & Fulginiti, 1971). "Functional pools" seem to be made up of recently synthesized catecholamines (Wise & Stein, 1969); Euler, 1971) which is released by nervous stimulation (Kopin, Breeze & others, 1968). If so, it is possible that MAO inhibition may prevent the degradation of catecholamine released by amphetamine, nicotine or cold, and keep the functional integrity of the adrenergic mechanisms involved in these processes.

The fact that inhibition of MAO by nialamide produces a significant increase in the number of CRs as compared with saline control groups and that it counteracts the depressive effects shown by the interaction of α-MT with amphetamine, nicotine or cold, represents additional pharmacological evidence in support of the hypothesis of a role of catecholamines in the learning process, and sustains the hypothesis that the effect of amphetamine and nicotine may be mediated by a common mechanism of adrenergic nature.

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