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α-Methyltyrosine: effects on fixed ratio schedules of reinforcement

SIR,—α-Methyltyrosine is an inhibitor of tyrosine hydroxylase (Nagatsu, Levitt & Udenfriend, 1964) and when administered to guinea-pigs causes a fall in tissue catecholamine levels without affecting 5-hydroxytryptamine (5-HT). α-Methyltyrosine causes a decrease in motor activity, rotorod performance and shuttle-box conditioned avoidance responding (Rech & Moore, 1965) as well as a decrease in conditioned avoidance responding in an operant situation (Hanson, 1965). These effects are attributed to a decrease in catecholamines in that the effects of α-methyltyrosine are decreased by pre-treatment with a monoamine oxidase inhibitor, which does not alter its brain levels (Moore & Rech, 1967a). In addition, the depression of the conditioned avoidance response is reversed by L-dihydroxyphenylalanine (Moore & Rech, 1967b); also, effects of reserpine and α-methyltyrosine on the conditioned avoidance response and motor activity are similar (Smith & Dews, 1962; Seiden & Carlsson, 1963). We now report the effect of α-methyltyrosine on operant behaviour utilizing positive reinforcement.

Six 80-day old, male, albino rats (Holtzman) were trained in a Lehigh Valley operant conditioning chamber on a fixed-ratio schedule of reinforcement (FR-10, i.e., every tenth lever press was reinforced with 0·01 ml of water) (Ferster & Skinner, 1957). Reinforcement contingencies were programmed by means of solid-state logic modules (Massey Dickinson Co.). Training continued until the total number of responses in a 30-min session did not exceed ±10% of the mean total number of responses from the five previous sessions. When animals reached this level of response, α-methyltyrosine (suspended in polyethylene-glycol-200 and saline, 1:1) or vehicle was injected (i.p.) 8 and 4 hr before the next daily session. One week later animals given the vehicle were given drug and vice versa.

Lever pressing performance was initially depressed by 36% during the first 4 min period (see Table 1). During subsequent time periods, performance was

TABLE 1. EFFECT OF α-METHYLTYROSINE ON LEVER PRESSING PERFORMANCE. Each value = mean % depression (± s.e.m.) calculated from each animal's previous day's performance.

	Time (min)						
Schedule	4*	8	12	16	20	24	Total
FR-10	36·2 ± 6·6	47·9 ± 6·9	56·9 ± 10·8	72·3 ± 12	77·4 ± 10	72·5 ± 10	62·6 ± 9
FR-20	36·1 ± 7·7	80·2 ± 6·8	92·2 ± 4·1	93·8 ± 4·5	99·4 ± 1	97·9 ± 2	84·6 ± 3

* All time periods significantly different at $P < 0.05$ except 4 min (Wilcoxon Rank Test).

depressed further. The same rats were then conditioned on an FR-20 schedule, and after they had reached the defined response level (3–4 weeks), α-methyltyrosine was again given. During the first 4-min period there was again a 36% depression of lever pressing. In this respect, the effect of the compound on the FR-10 and the FR-20 schedules is the same. However, during the later time periods the rats on the FR-20 schedule showed a greater depression of lever pressing which progressively increased. The rats did not appear sedated and consumed any water obtained by biting and sniffing of the lever. There was no observable effect in the vehicle-treated rats.

Untrained rats killed 6, 8 and 10 hr after the initial dose of α-methyltyrosine showed approximately the same reduction in brain catecholamines. [The animals were given two injections of α-methyltyrosine (2 × 75 mg/kg) 4 hr apart and brain dopamine and noradrenaline levels (μg/g ± s.e.m.) were: for dopamine 0·83 ± 0·06; 0·23 ± 0·02; 0·23 ± 0·01; 0·25 ± 0·05 at 0, 6, 8 and 10 hr after the first injection. For noradrenaline the respective figures were: 0·40 ± 0·03; 0·18 ± 0·02; 0·16 ± 0·01 and 0·17 ± 0·01.] Assay of brain noradrenaline (Bertler, Carlsson & Rosengren, 1958) showed a decrease of between 55 to 60% over the three time intervals studied: assay of brain dopamine (Carlsson & Waldeck, 1958) showed a decrease of between 70 to 72%.

The depression of lever pressing appears not to be a simple function of total brain catecholamine levels, since on both the FR-10 and FR-20 schedules the animals received the same dose of α-methyltyrosine and yet responded differently. Furthermore, the degree of depletion by the compound cannot explain the progressive nature of the depression. There is, therefore, either no involvement of catecholamines in the depression of lever pressing or the involvement is more complex, such as an interaction between the behavioural situation and a critical pool of amines. The progressive depression of the response may then be a function of the degree of interaction of the schedule contingencies and the animal's biochemical status (e.g. during the initial period of responding).

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