Behavioural effects of α-methyltyrosine administered in the diets of mice pretreated with a monoamine oxidase inhibitor

SIR,—Multiple injections of α-methyltyrosine produce behavioural depression in cats, rats and guinea-pigs (Hanson, 1965; Moore, 1966; Rech, Borys & Moore, 1966). Drugs which alter the steady-state levels of brain catecholamines modify the central actions of α-methyltyrosine. For example, reserpine and tetrabenazine enhance the behavioural depression (Rech, Carr & Moore, 1968), while monoamine oxidase inhibitors partially prevent (Moore & Rech, 1967a) and dopa reverses (Moore & Rech, 1967b) the behavioural effects of α-methyltyrosine in rats. These observations indicate that at least part of the acute depressant actions of the drug are secondary to its ability to deplete the brain of noradrenaline and dopamine.

Since α-methyltyrosine is insoluble in aqueous solutions at physiological pH it must be injected as a strong acidic or basic solution or as a suspension, and these are irritant. Johnson, Kim & others (1967) avoided its parenteral administration by adding it to the diet of mice and showed that the reduction of spontaneous locomotor activity in mice fed a 48 hr diet containing the drug was accompanied by a reduction in the brain levels of dopamine and noradrenaline.

Male albino mice (Spartan Farms) 25–30 g were maintained 8 per cage. At zero time a control ground diet (Wayne Lab-blox) or the same diet containing 0·3% α-methyltyrosine was added to the cages. At the same time the animals were given an intraperitoneal injection of saline or 10 mg/kg of the monoamine oxidase inhibitor pheniprazine. The mice were divided into 4 groups (6 cages/group): saline + control diet, pheniprazine + control diet, saline + α-methyltyrosine diet, pheniprazine + α-methyltyrosine diet. Twenty-four hr later the spontaneous locomotor activity of the mice was determined in circular actophotometer cages (Woodward Research Corp.). Two mice were placed in each cage; after 10 min for acclimatization, motor activity was recorded for 10 min. The mice were then killed by beheading and blood collected from the trunk into beakers containing heparin. Four brains were pooled and analysed for noradrenaline and dopamine (Moore & Rech, 1967a). Four plasma samples were pooled and analysed for α-methyltyrosine as described by Carr & Moore (1968).

Neither pheniprazine pretreatment nor the diet containing α-methyltyrosine significantly altered the food intake (Table 1). Although pretreatment with the monoamine oxidase inhibitor elevated the brain noradrenaline content it did not significantly alter motor activity (saline + control diet versus pheniprazine + control diet). After 24 hr on the diet containing the drug the motor activity and brain catecholamine levels of the animals were significantly reduced. In those

TABLE 1. EFFECTS OF α-METHYLTYROSINE IN MICE PRETREATED WITH A MONOAMINE OXIDASE INHIBITOR

Diet		Control		α-Methyltyrosine 0·3%	
Pretreatment	N	Saline	Pheniprazine	Saline	Pheniprazine
Food intake (g/g body wt)	6	0·152 ± 0·012	0·148 ± 0·004	0·159 ± 0·005	0·162 ± 0·006
α-MT intake (mg/kg)	6	—	—	480	486
Motor activity (counts/10 min)	24	598 ± 36	665 ± 39	246 ± 24*	416 ± 27*,†
Brain noradrenaline (μg/g)	12	0·37 ± 0·01	0·56 ± 0·02*	0·19 ± 0·01*	0·32 ± 0·01*†
Brain dopamine (μg/g)	12	0·75 ± 0·05	0·86 ± 0·04	0·31 ± 0·03*	0·40 ± 0·02*
Plasma α-MT (μg/ml)	12	—	—	7·0 ± 0·7	6·6 ± 0·4

Values represent the means ± 1 standard error as determined from 6 cages of 8 mice in each treatment. N, number of determinations.
* Significantly different from control diet and saline pretreament at $P < 0.01$.
† Significantly different from diet containing α-methyltyrosine and saline pretreament at $P < 0.01$.

animals that received the monoamine oxidase inhibitor and the α-methyltyrosine-containing diet, motor activity and brain amine levels were lower than corresponding control values. However, values for the spontaneous locomotor activity and the brain content of noradrenaline were significantly higher in the pheniprazine-α-methyltyrosine group than in saline-α-methyltyrosine group. Although pheniprazine partially blocked the behavioural depression and noradrenaline depletion it did not alter plasma levels of α-methyltyrosine. Thus the behavioural depression after a 24 hr diet containing α-methytyrosine appears to be related to the brain levels of catecholamines.

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The tensile strength of lactose tablets

SIR,—As part of an examination of the compaction properties of spray-dried and crystalline lactose, we have compared the tensile strengths of tablets prepared from the two forms of lactose, by means of the diametral compression test. This procedure was devised by Carneiro & Barcellos (1953) to assess the tensile strength of concrete and it has since been applied to coal (Berenbaum & Brodie, 1959); ceramics (Rudnick, Hunter & Holden, 1963); dental amalgam (Eden & Waterstrat, 1965) and dental gypsum plasters and stones (Earnshaw & Smith, 1966). Three size fractions and unfractionated samples of crystalline (B.D.H. Laboratory reagent grade) and spray-dried (McKesson Robbins) lactose, were used to prepare tablets, in the form of cylinders, 1·27 cm. in diameter, and approximately 0·3 cm thick. These tablets were compressed diametrically at a rate of 0·1 cm/min between the platens of an Instron Physical Testing Instrument using conditions that induced a uniform tensile stress across the diametral plane joining the two lines of contact of the specimen and platen, normal to that plane. The magnitude of the stress is given by the equation (Timoshenko, 1934; Froch, 1948).

$$\sigma x = \frac{2P}{\pi Dt}$$

where σx is the tensile stress, P the applied load and D and t the diameter and thickness of the specimen. The tensile strength can be calculated from the breaking load, by application of the above equation, provided failure occurs in tension. All the specimens tested met the requirements for tensile failure