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The role of dopamine in motor excitation of mice induced by brain catecholamine releasers

SIR,—Animals treated with monoamine oxidase inhibitors show intense behavioural excitation after the administration of drugs that release catecholamines in the brain. This excitation is currently interpreted as the effect of an excess of free and active amines reaching their receptors (Brodie, Pletscher & Shaw, 1956; Costa, Gessa, Kuntzman & Brodie, 1962; van Rossum & Hurkmans, 1963; Graeff, Garcia Leme & Rocha e Silva, 1965). However the specific role played by noradrenaline or dopamine in this phenomenon is still uncertain.

The experiments now presented suggest a predominant participation of dopamine in the psychomotor stimulation of mice after reserpine or α-methyl-*m*-tyrosine when given after a monoamine oxidase inhibitor.

Seventy male albino mice, 20–25 g, were divided into 7 groups for different drug treatments. In each experiment one pair of mice had its motor activity continuously registered during the 5 hr after the last drug injection by means of a photoelectric actometer (van Rossum & others, 1962). The treatment schedule and the results are summarized in Table 1. All drugs were dissolved in saline except reserpine (Serpasol, Ciba, Brazil) which was diluted in distilled water.

TABLE 1. INHIBITION BY α-METHYL-*m*-TYROSINE OF MOTOR STIMULATION CAUSED BY BRAIN CATECHOLAMINE RELEASE IN MICE

	Treatment (doses in mg/kg)	Activity counts*
I	Saline (i.p.) 15 min after MAOI†	3·92 ± 2·81
II	Reserpine (10, i.p.) 15 min after MAOI	60·26 ± 7·41
III	Methyltyrosine (160, i.v.) and after 5 hr, MAOI + reserpine (10, i.p.)	10·44 ± 7·14
IV	Methyltyrosine (160, i.v.) and after 24 hr, MAOI + reserpine (10, i.p.)	57·50 ± 3·71
V	Methyltyrosine (50, i.p. 15 min. after MAOI	38·98 ± 8·93
VI	Methyltyrosine (160, i.v.) and after 5 hr, MAOI + methyltyrosine (50, i.p.)	11·76 ± 4·78
VII	Methyltyrosine (160, i.v.) and after 24 hr. MAOI + methyltyrosine (50, i.p.)	36·72 ± 11·21

*Total number of impulses recorded during 100 min of maximal activity; figures represent the mean and standard error of 5 pairs of mice.
† Monoamine oxidase inhibitor: *N*-(1,4-Benzodioxan-2-yl)-*N*-benzylhydrazine tartrate (2596-IS, base-62%), 80 mg/kg i.p.

Five hr after the depleting dose of α-methyl-*m*-tyrosine (160 mg/kg, i.v.) there was a sharp reduction in the psychomotor stimulation induced by reserpine or methyltyrosine (50 mg/kg, i.p.) injected after monoamine oxidase inhibition; the response returned to control values 24 hr later. Data reported by Costa & others (1962) indicate that the dose of methyltyrosine employed (160 mg/kg, i.v.) gives an almost complete depletion of brain noradrenaline of several days' duration whilst dopamine is only transitorily decreased; the maximum dopamine depletion occurs around 4 hr after the injection and the normal concentration is almost restored 24 hr later.

Our results suggest that a normal dopamine store is the only requirement for the production of motor stimulation by catecholamine releasers; however, the

possibility of dopamine interacting with noradrenaline receptors in the brain (Carlsson, 1966) remains.

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On the mechanism of chlorpromazine-induced changes of cerebral homovanillic acid levels

SIR,—In various animal species, chlorpromazine and other neuroleptic drugs increase the concentration of the dopamine metabolite 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid) in the brain, especially in the extrapyramidal centres, without markedly interfering with the content of dopamine and 5-hydroxyindoleacetic acid (Andén, Roos & Werdinius, 1964; Gey & Pletscher, 1964; Juorio, Sharman & Trajkov 1966; Laverty & Sharman, 1965; Da Prada & Pletscher, 1966; Roos, 1965). Hydroxylation of tyrosine is thereby enhanced (Burkard, Gey & Pletscher, 1966). The question has been raised whether neuroleptics might enhance the formation of dopamine through a feedback mechanism due to blockade of dopaminergic receptors (Carlsson & Lindqvist, 1963; Gey & Pletscher, 1964; Da Prada & Pletscher, 1966). The results of the present experiments accord with this assumption and indicate that the storage sites of dopamine are possibly involved in the feedback mechanism.

Normal rats were injected i.p. with various psychotropic drugs (see Table 1). In addition, 10 mg/kg chlorpromazine was administered subcutaneously at various time intervals after intraperitoneal injection of 2·5 mg/kg reserpine. The animals were kept at an environmental temperature of 31–32° so that the rectal temperature remained normal within a range of ±1–2° during the course of the experiments. Homovanillic acid, 5-hydroxyindoleacetic acid (5-HIAA) and dopamine were measured in the brain stem (including basal ganglia, but without medulla oblongata and pons) with spectrophotofluorimetric methods (Andén, Roos & Werdinius, 1963; Carlsson & Waldeck, 1958; Pletscher, Burkard & Gey, 1964).

Neuroleptics of various chemical structures (chlorpromazine, chlorprothixene, haloperidol), in contrast to thymoleptics (imipramine, amitriptyline), tranquillisers (meprobamate, chlordiazepoxide, diazepam), and hypnotics (pheno-