Role of Catecholamines in the Amphetamine Excitatory Response

WHETHER amphetamine exerts its behavioural excitatory action in the brain directly or indirectly by interference or synergism with the catecholamines (noradrenaline and dopamine) is open to debate[1,2]. The advent of α-methyl *para*-tyrosine[3] (α-MPT), which inhibits the *in vivo* synthesis of 3,4-dihydroxyphenylalanine (DOPA)—the physiological precursor of the catecholamines—offers a new way of investigating this problem.

Spector *et al.*[3] showed that after treatment with α-MPT the content of noradrenaline in the brain and other organs gradually decreased, and after repeated doses it finally became impossible to detect noradrenaline. We found, using twelve rats, that even 3–5 h after one dose of α-MPT (75–200 mg/kg subcutaneously), amphetamine (3 mg/kg subcutaneously—referring to the *d*-amphetamine base) elicited little motor activity. The rats sat quietly and performed some grooming actions; with the lower doses, however, they also walked forwards. After repeated doses of α-MPT, even 6 mg of amphetamine/kg given subcutaneously was antagonized (Table 1).

Table 1. BEHAVIOURAL EFFECTS OF AMPHETAMINE AND *l*-DOPA IN RATS PRETREATED WITH REPEATED DOSES OF α-METHYL *para*TYROSINE

All rats received subcutaneously 100 mg/kg α-MPT 9, 6 and 3 h before treatment with amphetamine and DOPA

	Dose (mg/kg s.c.)	No. of rats	No. of rats showing stereotype behaviour*	Level of motor activity
Amphetamine	6	6	0/6	Low†
Amphetamine + *l*-DOPA	3 200	6	6/6	High‡
l-DOPA	400	6	0/6	Low§

* Constant sniffing, licking or biting of cage netting wire.

† Sat quietly most of the time. Performed some grooming and 50–70 min after amphetamine walked forward a little. Very little sniffing.

‡ Vigorous sniffing and biting for more than 30 min, walked forwards, backwards and circled about, but no grooming.

§ Sat or lay quietly, grooming, very little sniffing.

Amphetamine, when given alone, always produced marked hyperactivity and continuous, stereotype sniffing, licking or biting of the wire netting of the cage[2,4,5] (more than 200 rats were observed when doses of 1·5–30 mg/kg were given subcutaneously). With doses larger than 3 mg/kg, forward walking was completely abolished for a while; the rats performed their stereotype activity without moving, or they only walked backwards[4,5]. Grooming actions were not observed[5].

The experimental results in Table 1 strongly suggest that the antagonistic effect of α-MPT on amphetamine is due to the inhibition of DOPA-synthesis and not to some other action of the drug. Doses of up to 400 mg *l*-DOPA/kg given subcutaneously (nine rats treated) also had little effect on the gross behaviour of rats which had not received any pretreatment. A larger dose of *l*-DOPA (1,200 mg/kg given subcutaneously), however, produced hyperactivity and stereotype behaviour similar to that seen after amphetamine (ten rats)[6].

As inhibition of amphetamine-induced stereotype behaviour would seem to be a characteristic property of neuroleptic drugs[5,7], α-MPT may possess antipsychotic activity. Here it is interesting to note that α-MPT, like perphenazine[5], not only antagonized the abnormal stereotype activity but also simultaneously increased normal activities such as grooming and, in lower doses, forward walking.

Since this report was completed we have learned that Weissmann and Koe (*Life Sci.*, 4, 1037; 1965) have also observed the antiamphetamine effect of α-MPT, but were unable to reactivate the rats with DOPA. In our experiments, however, the rats became active 75–90 min after the injection of amphetamine + DOPA while Weissmann and Koe only observed their animals 60 min after the injection.

We thank Merck, Sharp and Dohme for a generous supply of α-MPT.

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Intraventricular Administration of Nalorphine to Mice implanted with Pellets of Morphine

WHENEVER nalorphine is administered to white mice implanted with a pellet of morphine (base) an 'abstinence syndrome' is produced[1]. Its well-defined symptomatology and characteristics have been reported elsewhere[2–4]; the action of several drugs on the abstinence syndrome has also been tested[5–7]. However, its genesis is still not well understood. Because of this, it was thought of interest to determine whether nalorphine injected by the intraventricular route can elicit the abstinence syndrome in tolerant mice.

Male and female white mice weighing 25–30 g were divided into several groups of five animals each. Some groups were used as controls, while a morphine pellet was implanted in each mouse of the other groups; the daily absorption ranged between 90 and 130 mg/kg (ref. 1). Drugs were dissolved in physiological saline and administered in volumes of 0·025 ml. Intraventricular injections were performed according to the method of Haley and McCormick[8] as modified by Adler[9]. The correct location of the injected material was confirmed by (1) histological investigation after administration of indian ink; (2) by the appearance of the signs observed by Haley and McCormick immediately after a simple ventricular puncture or after the administration of saline and drugs (stupor, changes in the tail position, hyperexcitability and even slight convulsions)[8]. Observation of the mice was discontinued 15–20 min after the intraventricular injection.

In control mice, intraventricular injection of nalorphine (25 and 50 μg/kg) produced immobility or hypomotility during the first 5 min, followed by the appearance of exophthalmus, catatonia, and restlessness alternating with normal behaviour. The higher the dose, the more accentuated were the symptoms. Larger quantities (100 μg/kg) induced depression. Intraventricular injection of morphine (50 μg/kg) induced immobility in control mice; after 10 min some tail rigidity and restlessness were observed. Doses of 500 μg/kg elicited convulsions followed by a typical morphine syndrome.

In tolerant mice, an intraventricular injection of nalorphine was given 7–10 days after the implantation of morphine. This period was considered suitable for the development of an important degree of tolerance to and physical dependence on the alkaloid[2]. Doses ranging between 0·62 and 300 μg/kg were used (Table 1). 3–4 min after the administration of nalorphine the mice were able to move along if intensely stimulated; if undisturbed they lay motionless for 10–15 min. Furthermore, soft stools, micturition and restlessness were observed in many groups; these symptoms may be characterized as a dubious abstinence syndrome. When 200 and 300 μg/kg of nalorphine were administered, movements and positions typical of a weak abstinence syndrome could be observed, together with the aforementioned signs. When the same quantity of nalorphine was administered in a final volume of 0·01