explanation of the cardiovascular actions of tyramine. In the present study, the vasodilator effect of tyramine was seen immediately after the intra-arterial administration and this effect was not altered in animals pretreated with reserpine (2·5 mg kg^{-1}, i.p. 24 h before). It was also found that repeated injection of tyramine failed to produce tachyphylaxis. All these findings suggest that released catecholamines from the storage sites are not responsible for vasodilator action of tyramine in perfused hindquarter experiments.

Recently in our laboratory it was observed that in the perfused mesenteric artery preparation, tyramine (50–150 μg, i.a.) elicited a dose-dependent vasoconstrictor effect (Fig. 2). These two different actions of tyramine may be due to the structural differences in the vascular bed. The mesenteric artery preparation consists of arteries and arterioles while the hindquarter preparation comprises precapillary resistance vessels as well as intact blood vessels. These results would suggest that the action of tyramine in the hindquarter preparation may be a balance between the direct vasoconstriction of arteriolar smooth muscle and vasodilatation of precapillary resistance vessels of the vascular bed.

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Amphetamine-induced stereotyped behaviour and brain concentrations of amphetamine and its hydroxylated metabolites in mice

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Recently, it has been reported that *p*-hydroxyamphetamine (POA) and *p*-hydroxynorephedrine (PONE) may be involved in the amphetamine-induced behavioural changes in the rat (Hitzemann & Loh, 1974; Taylor & Sulser, 1973) and these hydroxylated metabolites have been implicated in the amphetamine-induced psychosis in man (Änggård, Jönsson & others, 1973). However, amphetamine metabolism in the rat primarily involves aromatic hydroxylation producing POA and PONE (Dring, Smith & Williams, 1970), whereas oxidative deamination is the major metabolic route in man (Caldwell, Dring & Williams, 1972). On the other hand, the mouse has an amphetamine metabolic profile similar to that of man (Dring & others, 1970). However, Jori & Caccia (1975) found measurable concentrations of POA and PONE in mouse brainstem (only brain region examined) at 1 h after a single dose of 7·5 mg kg^{-1} (+)-amphetamine sulphate (i.p). This POA concentration was less than that in rat brainstem, hemispheres and cerebellum (entire brain examined) at 1 h after a single dose of 15 mg kg^{-1} (i.p.) (+)-amphetamine sulphate (Jori & Caccia, 1974), while Hitzemann, Loh & others (1973) did not detect either metabolite in mouse brain. As the mouse seems suitable for studying amphetamine-induced stereotyped behaviour (Peachey, Rogers & others, 1976) we wondered if there was a correlation between amphetamine-induced stereotypy in mice and brain levels of amphetamine, POA and PONE.

Male Swiss Albino mice (30–40 g), housed individually in wire cages, had free access to food and water and were kept at 22–24° with a 12/12 h light/dark cycle. The mice were allowed to acclimatize to the environment for 7 days. (+)-Amphetamine sulphate (10 mg kg^{-1}) was given intraperitoneally (i.p.) twice daily at a 6-h interval. Mice were rated over a 2-min period for the presence of gnawing-licking-sniffing (GLS) or self-mutilating behaviour at 30 min after (+)-amphetamine administration at which time stereotypy is maximal (Peachey & others, 1976). Groups of 5 mice each were rated behaviourally at 30 min after 1,5,11,17,23,29,35,41 and 49 drug administrations and decapitated. In the amphetamine time-course study, groups of 4 mice were killed at each of the following times: 2,10,15,45,60 and 90 min after 1 and 49 drug administrations. Brains were removed, frozen in liquid nitrogen and then stored at −20° until analysed. Amphetamine, POA and PONE were

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analysed using modifications of existing procedures (Änggård, Gunne & Niklasson, 1970; Belvedere, Caccia & others, 1973) with *p*-chlorophentermine and *p*-hydroxyphentermine as internal standards for amphetamine and the hydroxylated metabolites, respectively.

All brain samples were analysed for POA and PONE by a procedure with 5 ng g^{-1} sensitivity. No detectable amounts of either hydroxylated metabolite were found in the brains of mice up to 90 min after (+)-amphetamine administration to untreated and chronically treated animals. Since PONE appears to accumulate in noradrenergic nerve terminals (Lewander, 1971) and since the brainstem, hemispheres and cerebellum have appreciable noradrenergic innervation, it is conceivable that any PONE in mouse brainstem is a reflection of its concentration in hemispheres and cerebellum. Hence, in our study, one might have expected to find detectable amounts in mouse whole brain. In view of its long half-life (20 h) (Costa & Groppetti, 1970) and the twice daily administration of (+)-amphetamine in our study, it is interesting that no PONE was found in brains of mice given chronic drug treatment. The reasons for these discrepencies are not clear, although it should be emphasized that our results are for whole brain, whereas the work of Jori & Caccia (1974, 1975) pertains to discrete brain areas.

Behavioural data indicated that all mice engaged in GLS behaviour initially but 10 animals switched to self-mutilation during the course of chronic drug treatment. Amphetamine concentrations were determined in brains of mice that received single or multiple (+)-amphetamine administrations. The two brain samples selected from each group of 5 mice for amphetamine analysis were from animals engaged in the behaviour representative of that group. For the group of mice engaged in GLS, the range of brain amphetamine concentrations was 7·58–11·80 $\mu g\ g^{-1}$ with a mean and s.d. of 9·96 (1·51) $\mu g\ g^{-1}$; for mice engaged in self-mutilation, the amphetamine concentration range was 9·40–13·96 $\mu g\ g^{-1}$ with a mean and s.d. of 10·79 (1·57) $\mu g\ g^{-1}$. There was no significant difference between the amphetamine concentrations for the two groups of mice (Student's *t*-test). Also, the 90 min time-course study revealed that amphetamine brain concentrations were similar for mice receiving single or multiple drug administrations (half-life values of 46 and 53 min, respectively).

These findings demonstrate that amphetamine disposition in brain is similar for acute and chronic (+)-amphetamine administration to mice at a dosage that produces stereotyped behaviour. The type of stereotypy elicited by (+)-amphetamine seems to depend on factor(s) other than brain amphetamine concentrations and the presence of hydroxylated metabolites. Enhanced sensitivity of the dopaminergic nigrostriatal pathway, as a result of chronic (+)-amphetamine administration, in those mice that engaged in self-mutilation is a possible explanation that is compatible with the hypothesis of Klawans, Margolin & others (1975) of supersensitivity to amphetamine-induced stereotypy resulting from chronic drug administration.

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