The effect of tyramine on peripheral vasculature of the spontaneously hypertensive rat

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While studying the effect of vasoconstrictors on the peripheral vascular bed of spontaneously hypertensive (SH) rats, we found tyramine produced a fall in perfusion pressure in the perfused hindquarter preparation. Burn & Tainter (1931) reported that tyramine produced a fall in systemic arterial pressure and vasodilatation in the hindlimb of a cat treated with cocaine. According to Harakal, Sevy & Rusy (1964), local intra-arterial (i.a.) injections of tyramine in small doses in the dog increased renal, femoral and mesenteric vascular resistance without significantly altering the systemic haemodynamics. These two contradictory findings prompted us to investigate the action of tyramine in the rat perfused hindquarter preparation.

Male SH rats used were direct descendants of the original strain developed by Okamoto & Aoki (1963). Normotensive Wistar rats of same sex were used as control. Animals were anaesthetized with a combination of sodium pentobarbitone (20 mg kg^{-1}) and urethane (500 mg kg^{-1}). The hindquarter was perfused at a constant flow as described by Beck (1961). Blood from the proximal part of the abdominal aorta was forced by a peristaltic pump (Desaga) into the distal part of the aorta.

The systemic blood pressure and the perfusion pressure were measured with Statham P23Db pressure transducers and recorded through a physiological recorder (Hellige). The pump speed was so adjusted that the perfusion pressure and the systemic blood pressure were almost the same. Intra-arterial injections were made into the tubing towards the periphery. Heparin was injected (10 mg kg^{-1}) intravenously before cannulating the aorta.

Tyramine (25 to 150 μg, i.a.) produced a dose-dependent fall in perfusion pressure while the systemic blood pressure was not appreciably affected. This vasodilator effect of tyramine was more pronounced in SH rats than in normotensive rats (Fig. 1a, c). Tachyphylaxis was not observed in these experiments after repeated injections of tyramine (150 μg) (Fig. 1b). From these results it would appear that direct action of tyramine may be responsible for its vasodilator effect.

The effects of following antagonists given intra-arterially were studied using a fixed dose of tyramine (100 μg) which gave reproducible vasodilator responses: atropine sulphate, mepyramine maleate (May & Baker), methysergide bimaleate (Sandoz), phenoxybenzamine hydrochloride (SKF) and propranolol (ICI). The doses

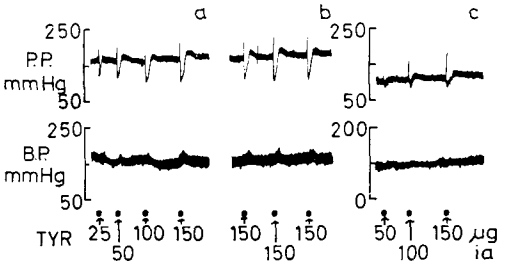

FIG. 1. Effect of tyramine (TYR) on the hindquarter perfusion pressure in anaesthetized rats. Tyramine injected intra-arterially (i.a.) in the hind limb region. Figures 1a and 1b depict the responses obtained in SH rats. Figure 1c depicts the responses in normotensive rats. B.P. = Blood Pressure. P.P. = Perfusion Pressure.

of the antagonists used were higher than those required for inhibiting the response of the agonist injected intra-arterially and elicited a transient fall in perfusion pressure. Six animals per group were used in each experiment.

The vasodilator effect induced by tyramine was not reduced either by phenoxybenzamine (500 μg) or propranolol (200 μg). This suggests that its action is not due to stimulation of α-and β-receptors of the blood vessels. Atropine (200 μg), mepyramine (200 μg) and methysergide (500 μg) failed to antagonize the tyramine action. This shows that cholinergic, histaminergic and serotoninergic mechanisms might not play any part in the vasodilator response of tyramine. This hypothesis does not agree with the work of Vanderipe & Kahn (1964) who stated that the vasodepressor response to tyramine is mediated through the release of histamine. Burn & Rand (1958) have shown that tyramine acts by releasing catecholamines from local storage sites. Many observations supported this hypothesis as an

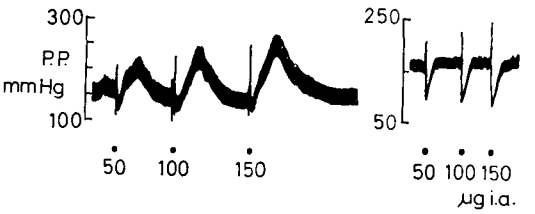

FIG. 2. Effect of tyramine injected intra-arterially (i.a.) on perfusion pressure (P.P.) of perfused mesenteric artery (L.H. tracing) and hindquarter (R.H. tracing) preparations in SH rats.

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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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