Amphetamine and stores of noradrenaline

SIR,—Tyramine is known to exert at least part of its pressor activity through the release of noradrenaline from its storage sites in postganglionic adrenergic nerve endings (Burn & Rand, 1958; Lockett & Eakins, 1961; Hertting, Axelrod & Patrick, 1961; Bhagat, 1963; 1964). Schumann & Philippu (1962) have further shown that tyramine and other indirectly acting sympathomimetic amines displace noradrenaline in almost stoichiometric proportions (mole by mole) from the isolated granules of the adrenal medulla. If this occurs also with noradrenaline in sympathetic postganglionic nerve endings then each injection of tyramine would decrease the noradrenaline content of the heart. But tyramine is also a good substrate for monoamine oxidase and is removed immediately from its stores probably mostly by oxidase action. If a sufficient time is allowed between successive injections of tyramine, the rate of replenishment of noradrenaline keeps pace with its release and consequently no tachyphylaxis develops. The other indirectly acting sympathomimetic amines, for example, amphetamine, which are not substrates for monoamine oxidase, may remain bound with the store, may prevent the entry of subsequent doses of indirectly acting amine (tyramine), and also the replenishment by more noradrenaline. Therefore, tachyphylaxis to these amines would be rapid and of a more permanent nature. This is consistent with the views of Blaschko (1962) that binding of amine at the site of storage may be responsible for the phenomenon of tachyphylaxis.

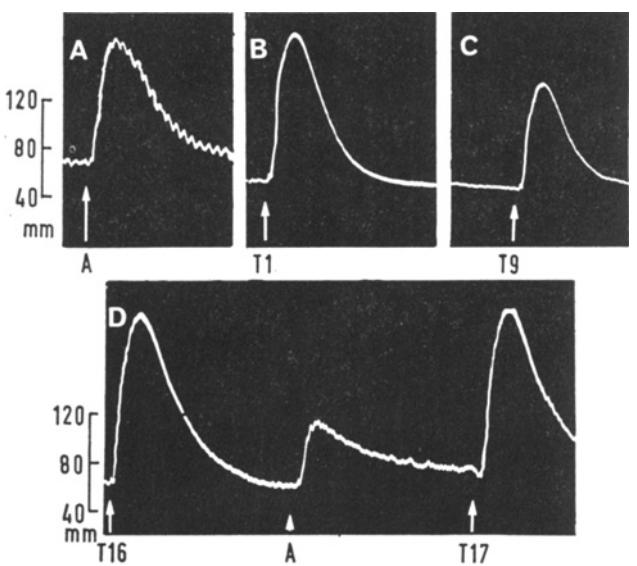

FIG. 1. A. Pressor response of a spinal cat (3·0 kg) to 200μg/kg of amphetamine (A). This result is typical of four experiments.
B, C, D. Pressor responses of a spinal cat (3·2 kg). Tyramine (800 μg/kg) was injected intravenously at 15 min intervals. The numerical sequence of tyramine doses (T) is indicated. After the 16th dose 200μg/kg amphetamine (A) was injected. This result is typical of four experiments.

Previous work from this laboratory (Bhagat, Kopin, Gordon & Booker, 1964; Bhagat, Gordon & Kopin, 1965) has shown that responses to repeated doses of

tyramine (800 μg/kg), administered intravenously to spinal cats, at first progressively diminish in size, that is, tachyphylaxis develops; with continued tyramine administration the response gradually returns to normal, that is, an escape from tyramine tachyphylaxis occurs. When the response to 800 μg/kg of tyramine has returned to normal, the response to exogenous noradrenaline is not significantly enhanced. The catecholamine content of the heart is diminished when tachyphylaxis is demonstrable (after the 9th dose), but is even further diminished when the response to tyramine has returned to normal (after the 16th dose). Biochemical evidence has been presented which indicates that tyramine administration accelerates noradrenaline synthesis, since tyramine is itself a precursor of noradrenaline (Chidsey, Kaiser & Lehr, 1964). This increased rate of synthesis appears to replenish an easily released noradrenaline store since escape from tachyphylaxis occurs, even though the total catecholamine content continues to diminish.

It is known that there is a cross tachyphylaxis between individual indirectly acting sympathomimetic amines. Presumably these amines act on the same store or pool of noradrenaline. It was therefore of interest to see whether the response to amphetamine returned to normal at a time when the response to tyramine had returned to normal (after 16th dose).

Cats of 2 to 3·5 kg body weight and of either sex were anaesthesised with ether and spinal preparations were set-up as described by Burn (1952). The arterial blood pressure was recorded from a carotid artery with a mercury manometer. All drugs were injected into a cannula tied into the femoral vein unless otherwise stated, and flushed in with 0·5 ml of normal saline.

The results indicated that at the 16th dose, the response to tyramine returned to normal (Fig. 1). Intravenous administration of 200 μg/kg of amphetamine showed a reduced response which was about 40 [±3·5 (4)] % of the normal. The response to tyramine after amphetamine was unaltered.

These results suggest that the mechanism by which amphetamine releases catecholamines is different from that of tyramine and may not be by an action on the same stores or pools of noradrenaline.

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