*Brit. J. Pharmacol.* (1965), **24**, 526–531.

# THE TACHYPHYLAXIS CAUSED BY MEPHENTERMINE AND TYRAMINE

BY

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(*Received August* 24, 1964)

The sympathomimetic action of mephentermine, like that of tyramine, is considerably reduced by procedures that deplete noradrenaline stores, such as administration of reserpine. We have, however, observed important differences between these two sympathomimetic amines in the speed with which tachyphylaxis to the pressor action develops, in their behaviour in dogs treated with reserpine before and after infusions of noradrenaline and in their action on the heart-lung preparation. Blaschko (1962) and Day & Rand (1963) concluded that the differences in behaviour, with regard to tachyphylaxis, between tyramine and α-methylated sympathomimetic amines could be explained by the resistance of the latter to attack by monoamine oxidase. The experiments reported in this paper suggest a more complex situation.

## METHODS

Mongrel dogs weighing 8 to 12 kg were anaesthetized with chloralose (150 mg/kg). In the heart-lung preparations the experimental dogs were anaesthetized with pentobarbitone (30 to 40 mg/kg) and the donors with chloroform. The blood pressure was measured from a common carotid artery by a mercury manometer and both cervical vagosympathetic trunks were cut. Heart rates were measured from electrocardiograph records. The heart-lung preparations were of the conventional type (Fawaz & Simaan, 1963). Reserpine was given as intraperitoneal injections of 0.5 mg/kg 48 hr and 24 hr before the experiment; such animals usually required less anaesthetic. Noradrenaline was estimated by the method described by Fawaz & Simaan (1963). Noradrenaline was used as the bitartrate, tyramine as the hydrochloride and mephentermine (Wyamine) as sulphate, and the doses quoted are expressed in terms of the bases. Injections into anaesthetized dogs were intravenous.

## RESULTS

### *The action of tyramine and mephentermine in dogs treated with reserpine*

In twelve dogs not treated with reserpine, the first injection of tyramine (2 mg) caused a rise in arterial pressure of $63 \pm 6.8$ mm Hg (mean and standard error). In sixteen similar dogs mephentermine (4 mg) caused a mean rise of $70 \pm 5.7$ mm Hg. But the intravenous injection of either tyramine or mephentermine caused only a slight rise in arterial blood pressure in dogs treated with reserpine (Table 1). When 2 mg of noradrenaline was infused over 50 min and tyramine (2 mg) or mephentermine (4 mg) was injected 5 to 10 min after the end of the infusion (when the blood pressure had reached a steady level), the pressor action was fully restored. The pressor action of mephentermine after the infusion was even greater than in normal dogs. These results are in harmony with those of Burn & Rand (1958) on spinal cats treated with reserpine. After the infusion of noradrenaline a

TABLE 1

THE PRESSOR EFFECTS OF TYRAMINE (2 mg) AND MEPHENTERMINE (4 mg) IN DOGS TREATED WITH RESERPINE BEFORE AND AFTER INFUSION OF 2 mg OF NORADRENALINE

Figures indicate mean and standard error of blood pressure increase in mm Hg. The number of experiments is in parentheses

| Before infusion | | After infusion of noradrenaline | |
|---|---|---|---|
| Tyramine | Mephentermine | Tyramine | Mephentermine |
| 20±3·8 (5) | | 90 ±9·4 | |
| 12±4·3 (4) | | | 145±15·5 |
| | | | 135±13·4 (6) |
| | 15±2 (4) | 5·5±0·3 | |
| | 28±1 (4) | | 12± 4 |
| 8±2 (6) | 13±2 | 6 ±1 | 3± 1 |

second dose of tyramine or mephentermine was usually much less effective than the first and slightly more effective than that before the infusion. When tyramine was given about 30 min after the end of the noradrenaline infusion, the rise in arterial pressure was not as great as when tyramine was injected 5 to 10 min after the infusion, but it was still significantly higher than before the infusion. However, when a single dose of mephentermine was given before the infusion of noradrenaline, the pressor effects of mephentermine or tyramine were not restored. When tyramine was given before the infusion the pressor effects were restored. When both tyramine and mephentermine were given before the infusion of noradrenaline, subsequent injection of either drug caused little rise in arterial pressure.

*Tachyphylaxis to the pressor actions of tyramine and mephentermine*

Tachyphylaxis to the pressor action of tyramine was difficult to demonstrate in the vagotomized dog during chloralose anaesthesia. Often there was no diminution in the pressor response to the tenth dose even when injections were given every 10 min. As a rule, however, the pressor response began to decline somewhat after the sixth injection. The situation with mephentermine was entirely different. Even the second injection caused a much smaller rise in pressure, and the fourth and subsequent injections produced a fall in blood pressure, which was proportional to the dose. Tachyphylaxis to the depressor action did not develop. Tachyphylaxis to the chronotropic action of mephentermine did not

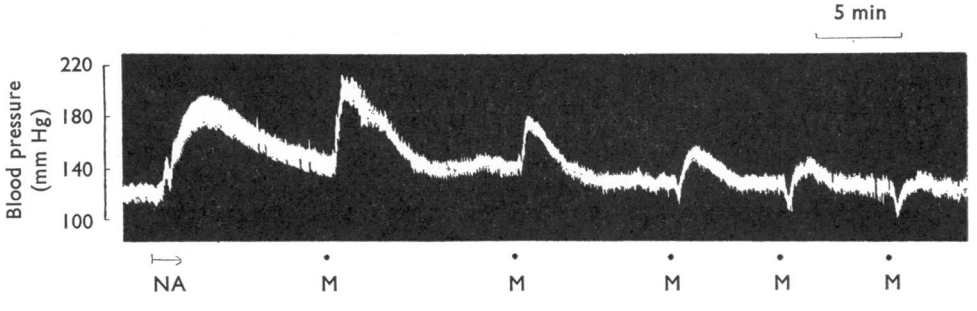


Fig. 1. Dog 10.5 kg. Records of arterial blood pressure. Repeated doses of mephentermine (M, 4 mg, intravenously, at black dots) were given during an infusion of noradrenaline (NA, 24 μg/min, starting at arrow), but tachyphylaxis developed nevertheless.

coincide with that to the pressor action, and the heart rate remained elevated for as long as 2 hr, at a time when injection of mephentermine caused only a fall in pressure. Tachyphylaxis to the pressor response of mephentermine was not prevented by massive noradrenaline infusions given before or after the development of tachyphylaxis. When mephentermine injections were given during a noradrenaline infusion, the pressor response disappeared just as in dogs which were not given an infusion (Fig. 1).

When tachyphylaxis had been produced to mephentermine the pressor response to α-methylated sympathomimetic amines such as ephedrine and methylamphetamine was greatly reduced but not that to tyramine. The interposition of a series of four or even six mephentermine injections between the first and second of a series of tyramine injections

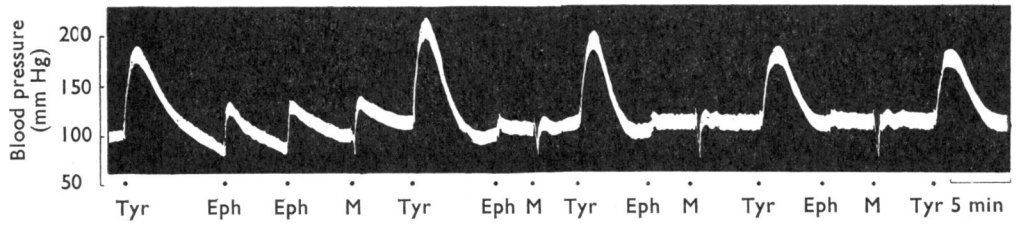


Fig. 2. Dog 9.6 kg. Records of arterial blood pressure. The pressor response to tyramine (Tyr, 2 mg, intravenously) was not greatly reduced by intravenous injections of mephentermine (M, 4 mg) or ephedrine (Eph, 0.6 mg first injection, 1.0 mg all others).

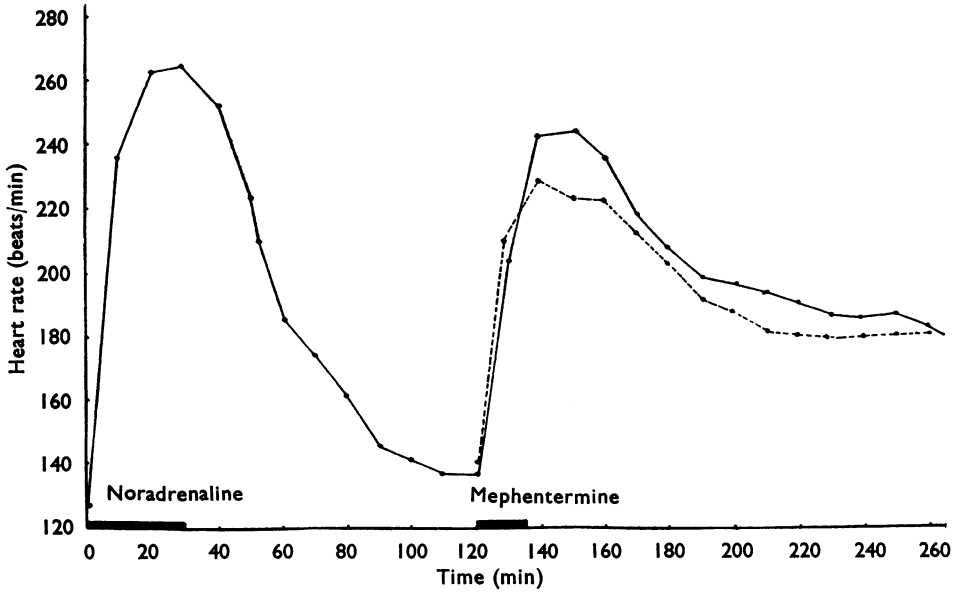


Fig. 3. Dog heart-lung preparations, mean changes in heart rate observed in eight experiments. The record shows the tachycardia on adding 0.75 mg of mephentermine to the venous reservoir over 15 min (interrupted line), and of preceding this by an infusion of 0.48 mg of noradrenaline (solid line). Drugs were added during the horizontal bars.

did not alter the normal progressive change in the response to tyramine (Fig. 2). On the other hand, a series of six tyramine injections given before the first dose of mephentermine much reduced its pressor action even though there was no tachyphylaxis to tyramine itself. In six such experiments the mean pressor response to mephentermine was 26% of that observed without prior treatment with tyramine.

*Action of mephentermine on the heart-lung preparation*

The addition of 0.75 mg of mephentermine to a dog heart-lung preparation in the course of 15 min caused a rapid large rise in heart rate (Fig. 3). The heart rate did not return to control even after 3 hr. This action resembles the acute effects of guanethidine, with the important difference that the latter causes a measurable reduction in the noradrenaline content of the right atrium (Fawaz & Simaan, 1963) while mephentermine did not. In seventeen heart-lung preparations the noradrenaline content of the right atrium 3 hr after the administration of mephentermine was $0.96 \pm 0.09$ $\mu$g/g (mean and standard error) compared with $0.85 \pm 0.08$ for seventeen control preparations. These results are in harmony with those of Davey & Farmer (1963) who found that tyramine, but not the $\alpha$-methylated amines like ephedrine and amphetamine, reduced the noradrenaline content of the guinea-pig isolated heart. It can also be seen from Fig. 3 that treatment of the heart-lung preparation with 0.5 mg of noradrenaline, a procedure known to increase the noradrenaline content of the right atrium, did not significantly alter the chronotropic response to mephentermine.

Tyramine has considerably less chronotropic activity than mephentermine on the normal dog heart-lung preparation, although it causes a larger rise of arterial pressure in the intact dog. A dose of 2 mg of tyramine is required to cause the same increase in heart rate as 0.75 mg of mephentermine. But while after tyramine the heart rate returns to control within about 30 min after stopping the infusion, after mephentermine it remains elevated for more than 3 hr.

## DISCUSSION

Tyramine and phenethylamine, as well as $\alpha$-methylated compounds such as amphetamine and mephentermine, belong to the group of sympathomimetic amines which act indirectly. They do not act unless they release noradrenaline from pre-existing stores.

Tachyphylaxis to tyramine develops more slowly than to the $\alpha$-methylated sympathomimetic amines such as $\alpha$-methyltyramine and amphetamine (Alles, 1933). After infusions of noradrenaline or a short period of rest the response to injection of tyramine and phenethylamine recovers, but not to that of their $\alpha$-methyl derivatives (Cowan, Cannon, Koppanyi & Maengwyn-Davies, 1961). Day & Rand (1963) and Davey, Farmer & Reinert (1963) reported that, under the influence of the monoamine oxidase inhibitor, nialamide, tachyphylaxis to the pressor action of tyramine develops as fast as to the $\alpha$-methylated sympathomimetic amines. Day & Rand (1963) state that the difference between tyramine and phenethylamine on the one hand, and their $\alpha$-methyl derivatives on the other, can be explained by the resistance of the $\alpha$-methyl derivatives to attack by monoamine oxidase, a conclusion also reached by Blaschko (1962). According to these authors the $\alpha$-methylated sympathomimetic amines first release noradrenaline from the stores, then block their own entry as well as that of subsequent doses of noradrenaline and other indirectly acting

sympathomimetic amines into the stores. We have also used similar arguments to explain certain actions of guanethidine, cocaine and indirectly acting sympathomimetic amines (Fawaz, 1963).

The results reported in this paper, however, cannot be explained by the hypothesis of Blaschko (1962) and Day & Rand (1963). We find that tachyphylaxis to mephentermine is not crossed to tyramine, while treatment with tyramine, even though no tachyphylaxis develops, markedly reduces the pressor response to mephentermine. Our results can be better explained on the assumption that in the adrenergic nerve endings to arteriolar smooth muscle, as in the heart, there are two noradrenaline stores—which may be interconnected—one large and one small. Mephentermine, a doubly α-methylated sympathomimetic amine, releases noradrenaline from the smaller store and also blocks the entrance of subsequent injections, including noradrenaline, to that store. Tyramine releases noradrenaline from both stores and does not block the entrance of sympathomimetic amines into the stores.

The right atrium of a heart-lung prepared from a dog treated with reserpine contains no noradrenaline. Infusion of 0.5 mg of noradrenaline in 30 min brings about a 10% repletion of the normal noradrenaline content. Treatment with guanethidine, but not reserpine, releases the noradrenaline taken up after the infusion, as shown by an increase in heart rate. Addition of guanethidine or reserpine to a normal heart-lung preparation causes an increase in heart rate, the action of guanethidine being greater. Guanethidine is active after the reserpine action subsides and *vice versa*. This led us to postulate that in the acute experiment guanethidine and reserpine act on different stores, guanethidine acting on the smaller store or the one to be first filled by the " repletion " experiment, although either drug could deplete both stores if given sufficient time (Fawaz & Simaan, 1963; Simaan & Fawaz, 1964).

In the present experiments, administration of mephentermine or tyramine, after infusion of 2 mg of noradrenaline into a dog treated with reserpine, probably leads to depletion of the " repleted " smaller store, and a second dose of either drug remains without significant pressor effect. Injection of mephentermine, but not tyramine, before the noradrenaline infusion prevents repletion of the store, and neither tyramine nor mephentermine have a pressor action after the infusion. This " blocking " action of mephentermine is also exhibited by cocaine (Fawaz, unpublished). In the intact animal, mephentermine acts on the smaller store, the rapid development of tachyphylaxis being due to lack of releasable noradrenaline. Tyramine, however, also has the bigger store to act on. Hence, tachyphylaxis develops slowly. In the isolated heart, tyramine, but not mephentermine, causes a measurable decrease in noradrenaline, presumably because the former acts on the larger store.

The explanation offered by Day & Rand (1963) for the observation that addition of nialamide causes tachyphylaxis to the pressor action of tyramine to develop as fast as to the α-methyl derivative does not fit with our observations. They state that nialamide, by inhibiting monoamine oxidase, prolongs the life of tyramine which then blocks its own entry into the stores. If this were the case, tachyphylaxis to the pressor action of mephentermine, which is a doubly α-methylated sympathomimetic amine and is thus expected to be immune to attack by monoamine oxidase, should be crossed to tyramine but this was never observed by us. We prefer the explanation offered by Davey *et al.* (1963) that nialamide blocks the entry of sympathomimetic amines to the stores; in other words

it exhibits a cocaine-like action. Actually the experiments of Davey *et al.* (1963) clearly indicate a cocaine-like action for nialamide.

The chronotropic action of mephentermine is prolonged, in contrast to its pressor action which soon fades away. In fact, one is hardly justified in talking of tachyphylaxis to the chronotropic action of mephentermine. The right atrium of a heart-lung preparation loses no noradrenaline after a 3-hr period of increased heart rate due to mephentermine; this is not the case with guanethidine under similar conditions (Fawaz & Simaan, 1963) or with tyramine acting on the guinea-pig isolated heart (Davey & Farmer, 1963). Here again, it is possible that mephentermine acts on the smaller store, so no measurable decrease in total noradrenaline content of the right atrium is observed. It is also possible that the smaller store is in close proximity to the pacemaker so that relatively small amounts of released noradrenaline could influence heart rate without affecting the noradrenaline content of the whole right atrium.

SUMMARY

1. Mephentermine, like tyramine, exhibits little or no pressor action in dogs treated with reserpine. The infusion of 2 mg of noradrenaline restores the pressor action of both amines, but not if an injection of mephentermine precedes the infusion.

2. Tachyphylaxis to the pressor action of mephentermine, unlike that to tyramine, develops extremely fast. Tachyphylaxis to mephentermine is not crossed to tyramine; but a few injections of tyramine, insufficient to produce tachyphylaxis to tyramine, markedly reduce the pressor response to mephentermine.

3. The action of mephentermine in increasing the heart rate of a dog heart-lung preparation is greater and more prolonged than that of tyramine; but, unlike tyramine, mephentermine does not reduce the noradrenaline content of the right atrium.

4. The suggestion is made that mephentermine liberates noradrenaline from, and blocks entry of sympathomimetic amines into, a small noradrenaline store while tyramine liberates noradrenaline from both small and large stores.

This work was supported by grants from the American Heart Association and the International Cardiology Foundation.

REFERENCES

ALLES, G. A. (1933). The comparative physiological actions of dl-β-phenylisopropylamines. 1. Pressor effect and toxicity. *J. Pharmacol. exp. Ther.*, **47**, 339–354.

BLASCHKO, H. (1962). Formation of pressor amines. In *Hypertension, Recent Advances*, ed. BREST, A. N. & MOYER, J. H., pp. 321–329. London: Kimpton.

BURN, J. H. & RAND, M. J. (1958). The action of sympathomimetic amines in animals treated with reserpine. *J. Physiol. (Lond.)*, **144**, 314–336.

COWAN, F. F., CANNON, C., KOPPANYI, T. & MAENGWYN-DAVIES, G. D. (1961). Reversal of phenylalkylamine tachyphylaxis by norepinephrine. *Science*, **134**, 1069–1070.

DAVEY, M. J. & FARMER, J. B. (1963). The mode of action of tyramine. *J. Pharm. Pharmacol.*, **15**, 178–182.

DAVEY, M. J., FARMER, J. B. & REINERT, H. (1963). The effects of nialamide on adrenergic functions. *Brit. J. Pharmacol.*, **20**, 121–134.

DAY, M. D. & RAND, M. J. (1963). Tachyphylaxis to some sympathomimetic amines in relation to monoamine oxidase. *Brit. J. Pharmacol.*, **21**, 84–96.

FAWAZ, G. (1963). Cardiovascular pharmacology. *Ann. Rev. Pharmacol.*, **3**, 57–90.

FAWAZ, G. & SIMAAN, J. (1963). Cardiac noradrenaline stores. *Brit. J. Pharmacol.*, **20**, 569–578.

SIMAAN, J. & FAWAZ, G. (1964). The chronotropic actions of guanethidine and reserpine on the isolated dog heart. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **247**, 452–455.