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THE LACK OF CROSSED TACHYPHYLAXIS BETWEEN TYRAMINE AND SOME OTHER INDIRECTLY ACTING SYMPATHOMIMETIC AMINES

BY

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In a previous paper (Day & Rand, 1963), it was shown that the pressor effects of the indirectly acting sympathomimetic amines phenylethylamine and tyramine exhibited a slowly developing and easily reversible tachyphylaxis on repeated injection. Tachyphylaxis to their α-methylated derivatives dexamphetamine and α-methyltyramine, however, developed rapidly and was only slowly reversible. Tachyphylaxis to dexamphetamine was crossed to phenylethylamine and tachyphylaxis to α-methyltyramine was crossed to tyramine. The rapid tachyphylaxis produced by α-methylated amines was attributed to their prolonged occupation of the noradrenaline storage sites due to their immunity from destruction by monoamine oxidase. Support for this concept was gained from the observation that in animals in which monoamine oxidase had previously been inhibited, phenylethylamine and tyramine behaved like their α-methylated derivatives and produced rapid tachyphylaxis. An essentially similar concept of tachyphylaxis to indirectly acting sympathomimetic amines has also been proposed by Blaschko (1962).

Recently, evidence has accumulated which casts some doubt on the validity of this simple concept. Fawaz & Simaan (1965) showed that the doubly α-methylated amine mephentermine produced rapid tachyphylaxis on the blood pressure of the anaesthetized dog, but the tachyphylaxis was poorly crossed to tyramine. Eble & Rudzik (1965), also in the dog, found a complete lack of crossed tachyphylaxis between dexamphetamine and tyramine. In their experiments, after marked tachyphylaxis to dexamphetamine, the pressor responses to tyramine were enhanced. Bhagat and co-workers (Bhagat, 1965a, b ; Bhagat, Gordon & Kopin, 1965) have made similar observations in the spinal cat. They found that large doses of tyramine injected at regular intervals produced a slowly developing tachyphylaxis. However, if the injections were continued the response to tyramine slowly returned to their initial height. This did not occur with dexamphetamine.

Various hypotheses have been proposed to explain this lack of crossed tachyphylaxis between tyramine and some other indirectly acting sympathomimetic amines. Thus, Fawaz & Simaan (1965) proposed that tyramine might release noradrenaline from a different storage site than mephentermine, while Bhagat *et al.* (1965) suggested that

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tyramine may accelerate noradrenaline synthesis possibly by itself acting as a noradrenaline precursor. Finally, Eble & Rudzik (1965) postulated that the enhanced responses to tyramine after dexamphetamine in their experiments may have been due to increased levels of circulating tyramine as a result of dexamphetamine delaying the destruction of tyramine.

The present investigation was undertaken to determine whether the basic concept of tachyphylaxis to indirectly acting amines as suggested by Blaschko (1962) and by Day & Rand (1963) is in error or whether tyramine has some action not shared by other indirectly acting sympathomimetic amines.

METHODS

Cat blood pressure

Cats were anaesthetized with intravenous chloralose (80 mg/kg) after induction with ether.

Spinal cats were prepared by the method of Burn (1952).

Blood pressure was recorded from a carotid artery by means of a mercury manometer ; drugs were dissolved in saline and injected into a femoral vein.

Contractions of the nictitating membrane

Contractions of the cat nictitating membrane were recorded with a frontal writing lever exerting a tension of about 1.5 *g* and with a magnification of about 8 times. In these experiments drugs were injected either intravenously into a femoral vein or close arterially into a small branch of the carotid artery which had previously been cannulated with flexible plastic tubing.

Pithed rat blood pressure

Rats (150–350 g) were anaesthetized with ether, or with pentobarbitone (60 mg/kg intraperitoneally) and then pithed by the method of Shipley & Tilden (1947). Blood pressure was recorded from a carotid artery using a Condon's mercury manometer and drugs were injected into a cannulated jugular vein.

RESULTS

The cats' blood pressure preparation

In 6 cats anaesthetized with chloralose it was shown that tachyphylaxis to mephentermine on the blood pressure occurred more rapidly than it did to tyramine when each substance was injected alternately, confirming the observations of Fawaz & Simaan (1965) in the dog. However, in every experiment some degree of crossed tachyphylaxis occurred provided that sufficient mephentermine was administered. This is shown in the experiment in Fig. 1 where alternate injections of mephentermine and tyramine were administered and the responses to tyramine declined more slowly than did those to mephentermine. After the fifth injection of mephentermine the pressor response to tyramine was reduced by approximately 50% compared with its original response. That this was due to partial crossed tachyphylaxis between the two substances is shown by the fact that the cardiovascular reactivity had not changed at the end of the experiment because the pressor action of noradrenaline and the depressor action of isoprenaline were virtually unaltered. In addition it was shown in other experiments that this dose of tyramine alone repeated at these intervals does not produce tachyphylaxis.

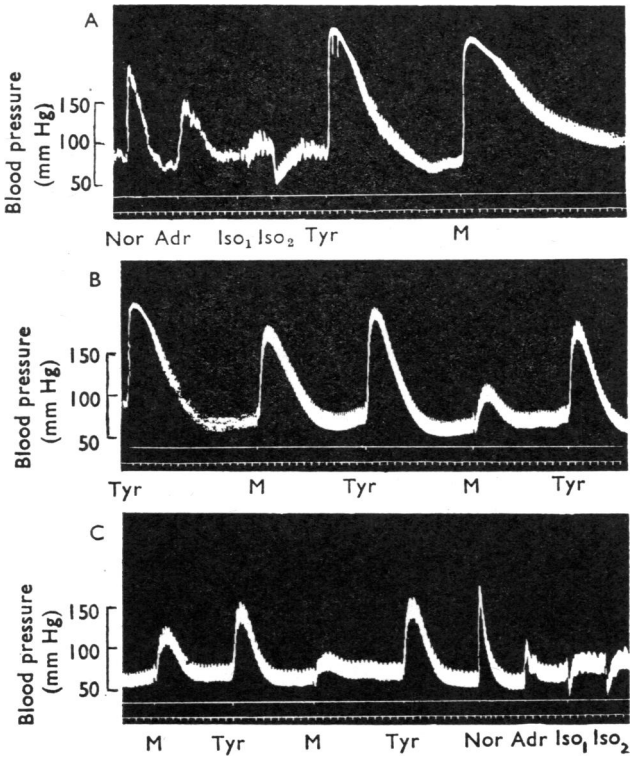

Fig. 1. Record of the blood pressure of a cat (2.6 kg) anaesthetized with chloralose. Noradrenaline 1 μg/kg (Nor), adrenaline 1 μg/kg (Adr) and isoprenaline 0.5 μg/kg and 1 μg/kg (Iso_1 Iso_2), tyramine 200 μg/kg (Tyr) and mephentermine 0.5 mg/kg (M) were all administered intravenously. The record is continuous; time-marker in this and subsequent figures is in min.

In two experiments it was shown that there was completely crossed tachyphylaxis between the pressor actions of mephentermine and phenylethylamine as was previously demonstrated for dexamphetamine and phenylethylamine (Day & Rand, 1963). In four of six other experiments it was shown that there was virtually no crossed tachyphylaxis beween tyramine and dexamphetamine and only partially crossed tachyphylaxis in the other two. In two of the former experiments after tachyphylaxis to dexamphetamine had occurred the responses to tyramine were enhanced as was shown in the dog by Eble & Rudzik (1965).

In other experiments similar results showing incompletely crossed tachyphylaxis between mephentermine and tyramine were obtained in 2 spinal cats and in 3 anaesthetized cats pretreated with the ganglion-blocking drug pentolinium (5–10 mg/kg). Thus the lack of complete crossed tachyphylaxis between the two substances is unlikely to be due to differences in the action of either substance on the central nervous system, autonomic ganglia or on cardiovascular reflexes.

Sympathetic β-receptor blocking drugs

One explanation for the lack of crossed tachyphylaxis between pairs of indirectly acting amines such as tyramine and mephentermine is that the amines may have differing relative affinities for cardiac and vascular noradrenaline stores. After tachyphylaxis to an amine producing its effects predominantly through release of cardiac catecholamine stores it might be expected that another amine acting mainly on vascular stores would produce an undiminished or only partly reduced response.

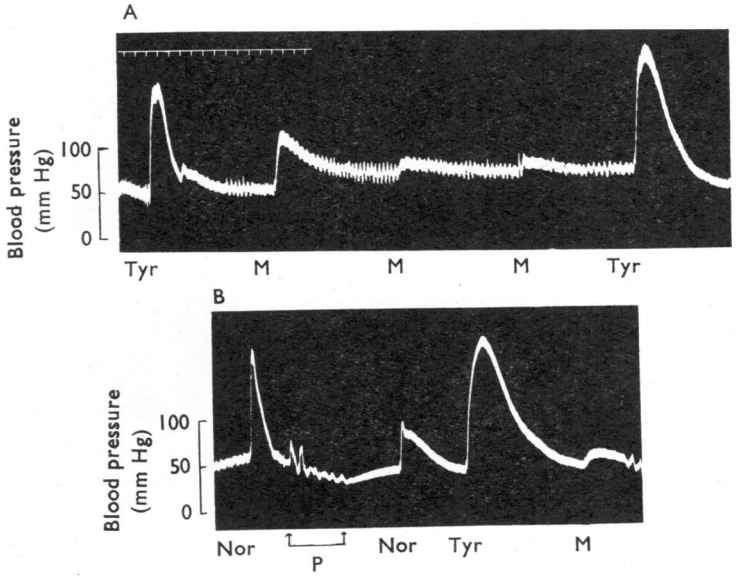

Fig. 2. Blood pressure of anaesthetized cat (2.4 kg) pretreated 1 hr previously with pentolinium (10 mg/kg). In A, intravenous doses of tyramine (0.5 mg/kg) at Tyr, mephentermine (0.5 mg/kg) at M. In B, noradrenaline (1 μg/kg) at Nor and pronethalol (10 mg/kg) at P.

This possibility was tested in 3 anaesthetized cats using tyramine and mephentermine by first abolishing cardiac effects with β-receptor blocking drugs. Figure 2 shows the result of one such experiment in a cat which had been pretreated with pentolinium (10 mg/kg) to abolish cardiovascular reflexes. The pressor response to mephentermine exhibited marked tachyphylaxis by the third dose, at which time the response to tyramine was unaffected. Pronethalol was then administered, and this considerably reduced the pressor effect of noradrenaline while the tyramine response was unreduced in height and increased in duration. Thus, in this experiment it is unlikely that the tyramine response after mephentermine tachyphylaxis was due predominantly to an action on the heart.

In two other experiments propranolol (5 mg/kg) was given at the start of the experiment; it considerably reduced the response to noradrenaline but had only a slight inhibitory action on both tyramine and mephentermine. In both these experiments mephentermine produced rapid tachyphylaxis which was incompletely crossed to tyramine. The fact that large doses of propranolol had little effect on the pressor action of either mephentermine or tyramine indicates that these amines probably produce their

effects predominantly by constricting the peripheral blood vessels rather than by stimulating cardiac β-receptors. Since there was the usual lack of crossed tachyphylaxis between mephentermine and tyramine after β-adrenergic receptor blockade it is unlikely that this can be due to a difference in affinities for cardiac and vascular noradrenaline stores between the two amines.

Effect on cat's nictitating membrane

In two cats anaesthetized with chloralose the actions of tyramine and mephentermine were studied on the nictitating membrane by injecting the amines into a branch of the carotid artery on the same side as the membrane under test. Figure 3 shows the result of one experiment. Intra-arterial injection of mephentermine caused a prolonged contraction of the nictitating membrane together with some spontaneous contractions. The contraction to tyramine following mephentermine was greatly potentiated, while those to phenylethylamine and noradrenaline were unaffected. The other experiment produced a similar result except that noradrenaline as well as tyramine produced an enhanced effect on the nictitating membrane after mephentermine.

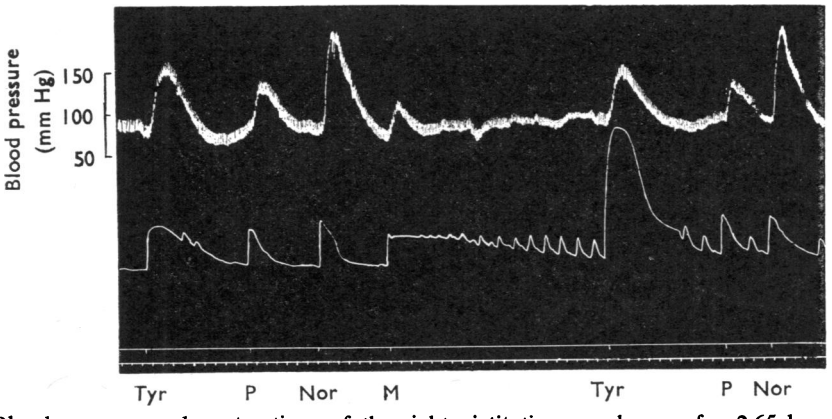

Fig. 3. Blood pressure and contractions of the right nictitating membrane of a 2.65 kg cat anaesthetized with chloralose. Drugs administered intra-arterially. At Tyr tyramine (200 μg), at P phenylethylamine (200 μg), at Nor noradrenaline (10 μg) and at M mephentermine (0.5 mg).

These experiments show that mephentermine potentiates the action of tyramine in contracting the nictitating membrane in doses which do not affect the response to phenylethylamine. This observation cannot be explained by the α-methylated mephentermine protecting tyramine from destruction by monoamine oxidase since phenylethylamine is also a substrate for this enzyme and its effects were not potentiated. It appears that on the smooth muscle of the nictitating membrane, as well as on that of the cardiovascular system, tyramine has some sympathomimetic action which is not shared by phenylethylamine and related indirectly acting sympathomimetic amines.

Experiments in pithed rats

The results obtained with this species were essentially similar to those obtained in the cat. The α-methylated amines, dexamphetamine and mephentermine, both produced

rapid tachyphylaxis on repeated injection in each of 12 preparations. There was crossed tachyphylaxis between dexamphetamine, mephentermine and phenylethylamine, but this was not extended to tyramine or α-methyltyramine. Figure 4 illustrates an experiment in which the fourth injection of dexamphetamine caused a pressor response of only 18 mm Hg compared with the initial response to this amine of 51 mm Hg. The tachyphylaxis was crossed to phenylethylamine but not to tyramine and the response to noradrenaline was unchanged.

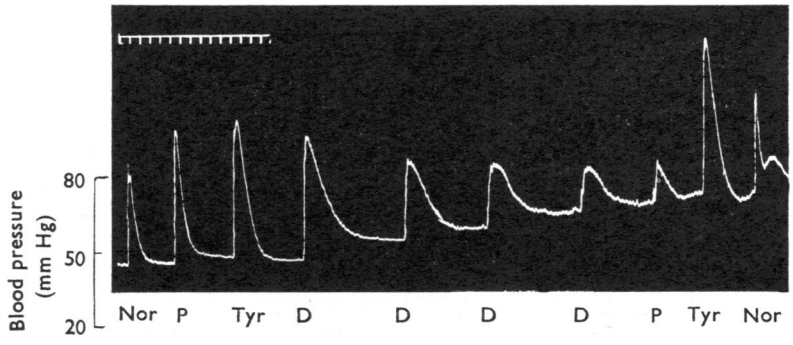

Fig. 4. Blood pressure of pithed rat (280 g). Intravenous doses of noradrenaline 50 ng (Nor), phenylethylamine 25 μg (P), tyramine 25 μg (Tyr) and dexamphetamine 25 μg (D).

The lack of crossed tachyphylaxis between tyramine on the one hand and mephentermine and dexamphetamine on the other was even more marked in the rat than in the cat. However, if dosage with one or other of the α-methylated amines was continued long enough then eventually the response to tyramine was reduced, without any loss of sensitivity to noradrenaline.

In three experiments tachyphylaxis to α-methyltyramine was produced and in each case this was crossed to tyramine, confirming previous observations (Day & Rand, 1963). In these experiments it was shown that the tachyphylaxis to α-methyltyramine was also crossed to phenylethylamine and to dexamphetamine. One of these experiments is illustrated in Fig. 5. The sixth injection of α-methyltyramine produced a very much

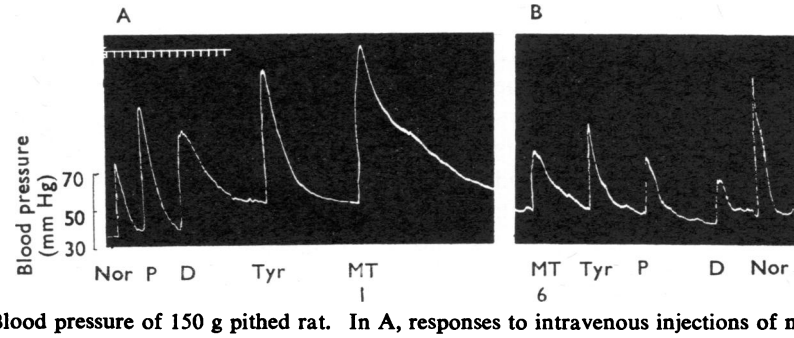

Fig. 5. Blood pressure of 150 g pithed rat. In A, responses to intravenous injections of noradrenaline 50 ng (Nor), phenylethylamine 50 μg (P), dexamphetamine 50 μg (D), tyramine 25 μg (Tyr) and α-methyltyramine 25 μg (MT1). In B, the response to the sixth injection of α-methyltyramine is shown (MT6) together with the second responses to the other control drugs.

reduced response as compared to the first response to this amine and the tachyphylaxis was crossed to the other indirectly acting amines tyramine, phenylethylamine and dexamphetamine. However, the response to the directly acting amine noradrenaline was enhanced at the end of the experiment, showing that there had been no loss of cardiovascular reactivity.

Effect of substances inhibiting the enzyme dopamine-β-oxidase

Tyramine is a good substrate for dopamine-β-oxidase (Goldstein & Contrera, 1962) and octopamine, its β-hydroxyl derivative, is present in tissues following tyramine administration. This accumulation of octopamine in the tissue is prevented by pretreatment with disulfuram which inhibits dopamine-β-oxidase (Musacchio, Kopin & Snyder, 1964). Since octopamine is known to have mainly direct sympathomimetic activity in the cat (Patil, Tye & LaPidus, 1965) it may be that the pressor responses to tyramine which persist after tachyphylaxis to either mephentermine or dexamphetamine are due to a direct sympathomimetic action of octopamine formed rapidly from tyramine. If this is so then, after inhibition of dopamine-β-oxidase, tyramine should exhibit crossed tachyphylaxis with other indirectly-acting sympathomimetic amines. This possibility was tested in cats and rats using disulfuram and its active metabolite diethyldithiocarbamate (DDC).

Experiments in cats

In three cats anaesthetized with chloralose rapid tachyphylaxis to mephentermine was induced by repeated injection at 15 min intervals. The tachyphylaxis was crossed in each case to phenylethylamine but not to tyramine. Disulfuram (300–400 mg/kg) was administered and 90–120 min later the sensitivity to tyramine and noradrenaline were retested. The results were the same in each experiment; one experiment is illustrated in Fig. 6. After mephentermine tachyphylaxis the responses to tyramine and noradrenaline were enhanced, while that to phenylethylamine was virtually abolished (Fig. 6 B). Two hours after disulfuram (300 mg/kg) had been administered the response to noradrenaline was reduced but that to tyramine was almost abolished (Fig. 6 C). This observation is consistent with the hypothesis that the response to tyramine after mephentermine tachy-

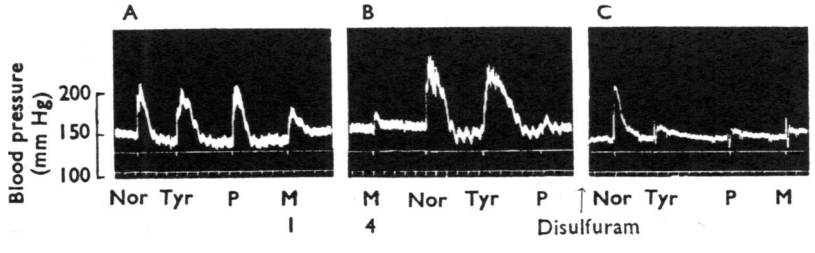

Fig. 6. Blood pressure of 2.65 kg anaesthetized cat. In A, control responses to noradrenaline 1 μg/kg (Nor), tyramine 100 μg/kg (Tyr), phenylethylamine 100 μg/kg (P) and mephentermine 300 μg/kg (M). In B, the response to mephentermine is the 4th to this amine and has produced tachyphylaxis which is crossed to phenylethylamine but not to tyramine or noradrenaline. Between B and C disulfuram (300 mg/kg) was administered intraperitoneally and 90 min later in C it has reduced the pressor responses to all the amines.

phylaxis is mediated, in the cat, by a β-hydroxylated derivative of tyramine. However, it was thought possible that disulfuram might have some other "anti-tyramine" effect possibly unrelated to β-oxidase inhibition. Accordingly, in two experiments control responses to tyramine, phenylethylamine and noradrenaline were obtained and were retested 60 min after the administration of disulfuram (300 and 400 mg/kg). Disulfuram markedly reduced the pressor responses to tyramine and phenylethylamine and slightly reduced that to noradrenaline. In these experiments tachyphylaxis was induced in one preparation to mephentermine and in the other to dexamphetamine. In both experiments the tachyphylaxis was crossed to phenylethylamine but not to tyramine.

In 5 similar experiments the sodium salt of diethyldithiocarbamate (DDC) was used instead of disulfuram. Doses of DDC up to 200 mg/kg produced only a slight impairment of the responses to tyramine, phenylethylamine and noradrenaline and did not influence the development of tachyphylaxis to mephentermine or dexamphetamine. In these experiments DDC did not affect the undiminished pressor response to tyramine following tachyphylaxis to mephentermine or dexamphetamine. Larger doses of DDC (400 mg/kg) produced a marked reduction in the responses to tyramine and phenylethylamine and a smaller impairment of noradrenaline responses.

Experiments in pithed rats

Disulfuram (300–400 mg/kg) was administered 1 to 16 hr before the acute experiment (5 expts.) or acutely after tachyphylaxis to mephentermine or dexamphetamine had been induced (8 expts.). In the majority of these experiments disulfuram treatment produced only a slight impairment of the responses to tyramine, phenylethylamine and noradrenaline. However, in 3 experiments only twice was crossed tachyphylaxis induced by treatment with disulfuram, once between tyramine and mephentermine and once between tyramine and dexamphetamine. In the other 11 experiments the tyramine response was either virtually unaffected or potentiated after tachyphylaxis to mephentermine or dexamphetamine. Figure 7 A shows the result of one of the two experiments; a rat pretreated with disulfuram in which tachyphylaxis to mephentermine was crossed to tyramine. Figure 7B shows the result of an identical experiment in which tachyphylaxis to dexamphetamine was not crossed to tyramine. In both experiments illustrated in Fig. 7 the sensitivity to noradrenaline was not appreciably altered at the end of the experiment.

In 6 other experiments DDC was used instead of disulfuram with similar results except the intravenous DDC (400 mg/kg) produced a greater impairment of the responses to direct and indirect amines than did disulfuram. In every experiment the response to tyramine was not appreciably further altered after marked tachyphylaxis to either mephentermine or dexamphetamine had been induced.

The above results using disulfuram and DDC provide indirect evidence that the pressor response to tyramine which persists after tachyphylaxis to either mephentermine or dexamphetamine is caused by tyramine itself and is not mediated *via* a β-hydroxylated derivative of tyramine. However no direct measurement of dopamine-β-oxidase activity has been performed in these experiments and in addition it is possible that repeated administration of sympathomimetic amines in these experiments may have competitively antagonized the enzyme inhibitor as in the experiments of Musacchio, Goldstein,

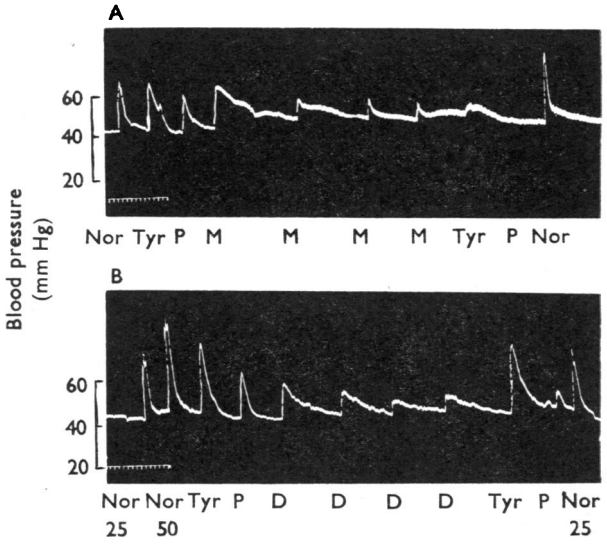

Fig. 7. Blood pressure records from two pithed rats pretreated 2 hr before pithing with disulfuram 400 mg/kg given intraperitoneally. In A, 210 g rat, tachyphylaxis to mephentermine 200 μg (M) was crossed to tyramine 25 μg (Tyr) and to phenylethylamine 25 μg (P) but not to noradrenaline 25 ng (Nor). In B, 206 g rat, tachyphylaxis to dexamphetamine 25 μg (D) was crossed to phenylethylamine 25 μg (P) but not to tyramine 25 μg (Tyr) nor to noradrenaline 25 ng (Nor).

Anagnoste, Poche & Kopin (1966). For these reasons further experiments were conducted to ascertain whether the response to tyramine following tachyphylaxis to mephentermine or dexamphetamine could possibly be due to a direct effect of octopamine formed from tyramine.

Experiments using the β-hydroxyl derivatives of tyramine and phenylethylamine

In the rat 1-octopamine was slightly more potent than tyramine whereas dl-phenylethanolamine was of similar potency to phenylethylamine (Fig. 8A). After cocaine treatment the responses to phenylethylamine and tyramine were markedly reduced, the

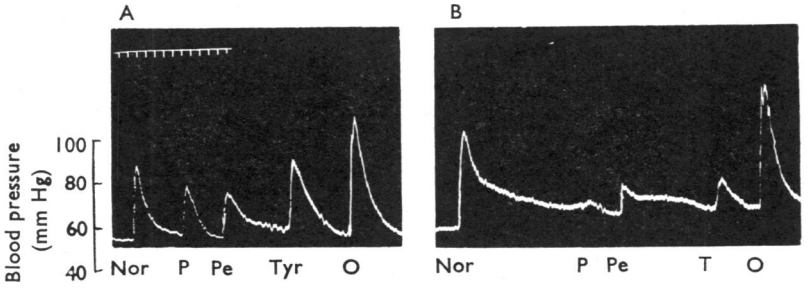

Fig. 8. Blood pressure of 215 g pithed rat. In A, control responses to noradrenaline 25 ng (Nor), phenylethylamine 25 μg (P), dl-phenylethanolamine 25 μg (PE), tyramine 25 μg (Tyr) and 1-octopamine 25 μg (O). In B, same drugs injected 90 min after the intraperitoneal administration of cocaine 10 mg/kg.

response to phenylethanolamine was slightly reduced and that to l-octopamine was unaffected (Fig. 8B). Thus, in this species l-octopamine is apparently directly-acting since it is not reduced by cocaine treatment.

In cats anaesthetized with chloralose the β-hydroxylated derivatives of phenylethylamine and tyramine were each found to be slightly less potent pressor substances than the respective non β-hydroxylated amines.

DISCUSSION

The observation made previously that the rapid tachyphylaxis to the pressor effects of dexamphetamine and α-methyltyramine is crossed to their respective non α-methylated amines (Day & Rand, 1963) has been confirmed here. However, the more recent report that tachyphylaxis to dexamphetamine or to the related amine mephentermine is only poorly or not at all crossed to tyramine (Bhagat 1965a, b ; Bhagat *et al.*, 1965 ; Eble & Rudzik, 1965 ; Fawaz & Simaan, 1965) has also been confirmed.

Various possible mechanisms to account for this latter phenomenon have been investigated. The pressor response to tyramine after tachyphylaxis to mephentermine or dexamphetamine persisted in the presence of effective doses of sympathetic β-receptor blocking agents, ganglion-blocking drugs and also in pithed and spinal animals. Thus, it seems unlikely that the phenomenon can be accounted for on the basis of differential effects of the amines on cardiac and vascular noradrenaline stores, on autonomic ganglia or on cardiovascular reflexes. In addition the responses to tyramine and phenylethylamine on the cat nictitating membrane were affected differently by an injection of mephentermine, tyramine being markedly potentiated while phenylethylamine was unaffected. This observation is consistent with the differences between the responses to these substances after tachyphylaxis to mephentermine or dexamphetamine noticed in the blood pressure experiments and suggests that the lack of crossed tachyphylaxis between tyramine and amphetamine-like drugs may extend to smooth muscle other than that of the cardiovascular system.

A further possibility which has been explored is that tyramine may be metabolized after injection into a more potent pressor substance. It is known that tyramine is a good substrate for dopamine-β-oxidase (Goldstein & Contrera, 1962) and that the β-hydroxylated derivative octopamine has mainly direct sympathomimetic activity in the cat (Patil *et al.*, 1965). However, the results obtained in the present study do not support this concept. In the first place octopamine is only slightly more potent as a pressor amine than tyramine in the rat and is actually less potent in the cat. In addition the dopamine-β-oxidase inhibiting substances disulfuram and DDC did not regularly produce crossed tachyphylaxis between tyramine and either mephentermine or dexamphetamine. In the few experiments in which, after dopamine-β-oxidase inhibition, tyramine produced crossed tachyphylaxis to amphetamine-like drugs it was impossible to preclude the possibility that the effect was due to a general decrease in cardiovascular reactivity. Bhagat (1965b) claimed that disulfuram did not itself reduce the pressor response to tyramine in his experiments. However, in the present experiments both disulfuram and DDC caused a considerable decrease in the pressor responses to both direct and indirect sympathomimetic amines. If the pressor response to tyramine after dexamphetamine tachyphylaxis is due to octopamine formation then it is necessary to postulate that

β-hydroxylation is very rapid and virtually complete. The available evidence suggests that this may be the case ; Musacchio, Kopin & Weise (1965) showed that in rats injected with tritiated tyramine and killed 4 min later about two-thirds of the tritiated amine recovered from the heart was in the form of octopamine. However, Iversen (1966) working with isolated perfused rat hearts found that at the end of 5 min infusion with α-methyltyramine less than 5% was converted to α-methyloctopamine.

Tyramine is a precursor of noradrenaline (Chidsey, Kaiser & Lehr, 1964) and it might be argued that only a small proportion of a tyramine dose need be converted to noradrenaline to yield an apparently undiminished response to tyramine after tachyphylaxis to other indirectly-acting amines. However, there are three pieces of evidence which together make this mechanism unlikely. Firstly, the lack of effect of dopamine-β-oxidase inhibiting drugs on the tyramine response after dexamphetamine or mephentermine tachyphylaxis. Secondly, the shape of the response resembled that to tyramine rather than noradrenaline and thirdly the response was reduced by cocaine showing it to be probably indirect in nature.

Another possibility proposed by Eble & Rudzik (1965) to explain the persistence of tyramine pressor responses after dexamphetamine tachyphylaxis, is that dexamphetamine increases the circulating level of tyramine by delaying its inactivation. It is well known that the main metabolic pathway for tyramine in the body is deamination by monoamine oxidase. However, Day & Rand (1963) showed that after inhibition of monoamine oxidase with nialamide the rate of onset of tachyphylaxis to tyramine was greatly increased. Moreover, α-methyltyramine which is itself immune to amine oxidase produces rapid tachyphylaxis which is crossed to tyramine. Thus, it would appear unlikely that the persistence of the tyramine response after dexamphetamine tachyphylaxis is due to an action of dexamphetamine on monoamine oxidase.

The evidence outlined above suggests that the lack of crossed tachyphylaxis between tyramine and its α-methyl derivative on the one hand and dexamphetamine, mephentermine and phenylethylamine on the other is due to some differing mechanism of noradrenaline release between these groups of amines at the level of the noradrenaline stores within the sympathetic nerve endings. The biochemical evidence in favour of at least two functionally distinct noradrenaline stores is now considerable and has been reviewed by Zaimis (1964). Fawaz & Simaan (1965) have suggested that mephentermine and tyramine may release noradrenaline from different stores. It would appear from the present results that phenylethylamine and dexamphetamine may also release noradrenaline from the same store as mephentermine, and α-methyltyramine evidently acts on the same store as tyramine. Another possibility is that the storage site for noradrenaline upon which both groups of indirect amines act is homogeneous but that they cause release by some differing mechanism. In either case there is considerable evidence that there is some overlap between the actions of all the indirectly acting amines and therefore possibly in the physiological functioning of the noradrenaline stores. For instance, in the present experiments it was shown that if dosage with dexamphetamine or mephentermine were continued long enough then responses to tyramine were eventually reduced without any reduction in the responses to noradrenaline. Bhagat (1965b) showed in the cat that there was a measure of crossed tachyphylaxis between dexamphetamine and tyramine since dexamphetamine hastened the development of tyramine tachyphylaxis. Fawaz & Simaan

(1965) made a similar observation in the dog ; at the time of complete loss of responsiveness to mephentermine the tyramine response was hardly reduced. However, pretreatment of dogs with several doses of tyramine themselves too small to cause tachyphylaxis, caused a reduction in the subsequent response to mephentermine. Similarly in the present experiments tachyphylaxis to α-methyltyramine was crossed to phenylethylamine and dexamphetamine as well as to tyramine.

It has recently been shown that in reserpinized animals the residual pressor responses to tyramine produce rapid tachyphylaxis which is crossed to dexamphetamine (Eble & Rudzik, 1966). It appears that reserpine is capable of disrupting the discrete nature of the noradrenaline stores such that all indirectly acting substances cause release of noradrenaline from a common pool.

The concept of direct and indirectly acting sympathomimetic amines proposed by Burn & Rand (1958) has received wide support and confirmatory evidence has been obtained by many workers. The results of recent studies including the ones presented here suggest that it may be necessary to extend this classification since it appears that indirectly acting amines may produce their effects by at least two distinct mechanisms.

SUMMARY

1. The effect of mephentermine and dexamphetamine on the blood pressure shows rapid tachyphylaxis of the responses when repeated injections of these amines are administered to anaesthetized and spinal cats and to pithed rats. The tachyphylaxis to these substances is mutually crossed and crossed to phenylethylamine but not to tyramine or to noradrenaline.

2. The lack of crossed tachyphylaxis between tyramine and the other indirectly acting amines occurs in cats treated with pentolinium and/or with sympathetic β-blocking drugs.

3. Crossed tachyphylaxis between tyramine and dexamphetamine and mephentermine occurred in some animals treated with disulfuram or diethyldithiocarbamic acid to inhibit the enzyme dopamine-β-oxidase. However, this occurred in a minority of such experiments and could have been due to a generalized reduction in cardiovascular reactivity caused by these enzyme inhibitors.

4. Experiments with 1-octopamine, the β-hydroxyl derivative of tyramine, suggested that the lack of crossed tachyphylaxis between tyramine and the other indirectly acting amines was not due to formation of this substance.

5. It is suggested that tyramine releases noradrenaline from a different storage site than dexamphetamine, mephentermine and phenylethylamine but that the two stores may be functionally connected.

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