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AN INVESTIGATION OF THE ACTION OF TYRAMINE AND ITS INTERRELATIONSHIP WITH THE EFFECTS OF OTHER SYMPATHOMIMETIC AMINES

BY

P. A. NASMYTH

From the Department of Pharmacology, St. Mary's Hospital Medical School, Paddington, London, W.2

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Choline 2,6-xylyl ether potentiated the sympathomimetic effects of tyramine and adrenaline in anaesthetized and spinal cats; the effects of noradrenaline were not significantly affected. The pressor activity of tyramine was also potentiated by the drug in reserpine-treated spinal cats and in pithed rats. The acute intravenous injection of reserpine in pithed rats potentiated pressor responses to tyramine, but depressed those to adrenaline and noradrenaline. During the intravenous infusion of noradrenaline in spinal cats and pithed rats the pressor responses to tyramine were increased, whilst those to adrenaline and noradrenaline were decreased. Infusion of isoprenaline in a spinal cat depressed responses to tyramine and noradrenaline, but potentiated those to adrenaline. A lower rate of infusion of isoprenaline in the same animal subsequently potentiated adrenaline and noradrenaline, but continued to depress tyramine. These results are held to be inconsistent with the view that the sympathomimetic effects of tyramine are produced entirely by the release of catechol amines.

In 1910 Barger & Dale showed that the sympathomimetic amines differed from one another in potency and in their ability to produce inhibitory effects. The reasons for these differences have remained somewhat obscure, but Barger & Dale were able to show some relationship between the chemical structure and the potency or the quality of the effect. There are not only quantitative differences between the sympathomimetic amines but also differences in the effects of other drugs upon their actions. For example, in 1910, Fröhlich & Loewi showed that cocaine potentiated the action of adrenaline, whereas Tainter & Chang (1927) showed that the same drug inhibited or abolished the effects of tyramine. In 1939 MacGregor suggested that the potentiation of adrenaline by cocaine was due to the ability of the local anaesthetic to inhibit amine oxidase and that it reduced the action of tyramine by preventing it from combining with the receptors. Neither Bacq (1949) nor Burn & Rand (1958a) believe this to be so.

Carlsson, Rosengren, Bertler & Nilsson (1957) noted that tyramine was without pressor activity in cats pretreated with reserpine. Burn & Rand (1957, 1958a, 1958b), investigating the effects of tyramine and other drugs in cats, dogs and rabbits treated with reserpine, concluded that several drugs, including tyramine, produced sympathomimetic effects by releasing noradrenaline from stores in sympathetically innervated

tissues. This hypothesis received much support; for example, Schumann (1960) showed that the rate at which catechol amines were lost from adrenal medullary cells, suspended in saccharose phosphate buffer solution at 37° C, was greatly increased by tyramine. Von Euler (1960) made similar observations on granules isolated from sympathetic nerves. Lockett & Eakins (1960a) claimed that the intravenous injection of tyramine in anaesthetized cats having their adrenals tied off and autonomic ganglia blocked with hexamethonium caused the appearance of adrenaline and noradrenaline in the abdominal aorta, although Vane (1960), using a different technique, was unable to find any evidence for a release of catechol amines into the blood stream.

The hypothesis that tyramine exerts its sympathomimetic effects by releasing noradrenaline from stores in sympathetically innervated tissues is an attractive one, because it satisfactorily explains the differences between the actions of adrenaline and noradrenaline, on the one hand, and tyramine on the other, before and after the administration of reserpine or cocaine. However, the results obtained in the experiments described below are difficult to reconcile with the hypothesis, and indicate that tyramine has sympathomimetic actions of its own which are not related to the release of adrenaline or noradrenaline.

METHODS

Cats were anaesthetized by the intravenous injection of 80 mg/kg of chloralose using a 10% solution in polyethylene glycol 200. Pentobarbitone (12 mg/cat) was mixed with each injection of chloralose.

Ether anaesthesia alone was used in animals which were to be pithed or spinalized.

Blood pressure was recorded with a mercury manometer connected to a carotid artery, or to a femoral artery when nictitating membrane contractions were to be recorded. The manometer used to record the blood pressure of rats was similar to that described by Condon (1951).

Records of contraction of the nictitating membrane. Measurements in cats were made with an isotonic frontal writing lever. A load of 2 g was applied to the membrane and its contractions were magnified 10 times.

Operative procedures. Spinal cats were prepared by dividing the spinal cord at the level of the second cervical vertebra and completely destroying the brain by pushing a brass rod of 4 mm diameter through the foramen magnum. After withdrawing the rod, the foramen was plugged with plasticine and a small cork.

Rats were pithed by pushing a no. 14 knitting-needle through the orbit, destroying the brain, and then the spinal cord by continuing to push the needle through the foramen magnum and down the vertebral column. The needle was left *in situ* to minimize bleeding. All pithed rats were pretreated with an intraperitoneal injection of 2 mg of atropine to minimize the excessive secretion of mucus caused by ether anaesthesia.

Drug solutions and injections. All drugs were dissolved in normal saline with the exception of reserpine, which was dissolved in 20% ascorbic acid solution to a strength of 10 mg/ml., and chloralose, which was dissolved in polyethylene glycol 200. With the exception of those used to produce anaesthesia or depletion of catechol amines, all drugs were injected into the femoral vein. Chloralose was injected into the vena cephalica.

Doses of all drugs are expressed in terms of base with the exception of tyramine, which is in terms of the hydrochloride. To avoid tachyphylaxis, doses of tyramine were given at intervals greater than 8 min; usually there was an interval of 15 to 20 min between doses.

Chronic reserpine treatment. Two injections of reserpine were given slowly into the vena cephalica under light ether anaesthesia. The first dose of 2.5 mg/kg was followed 24 hr later by a dose of 5 mg/kg. The animals were taken for experiment 24 hr after the second injection.

RESULTS

Effects of choline 2,6-xylyl ether on responses to sympathomimetic amines

Anaesthetized cats. In 9 cats anaesthetized with chloralose the effects of tyramine on the blood pressure and nictitating membrane responses were observed. After an intravenous injection of 5 mg/kg of choline 2,6-xylyl ether (T.M.10), the blood pressure responses to tyramine (0.3 to 1.4 mg) were potentiated both in height and duration. Maximal potentiation occurred about 40 min after the injection of the choline 2,6-xylyl ether, usually before the response of the nictitating membrane to nerve stimulation had been completely blocked. The potentiating effects of the ether lasted for at least 2 hr.

The response of the nictitating membrane to tyramine was considerably potentiated in 7 of the experiments, but usually at a later stage than the potentiation of the blood pressure response (Fig. 1). In two instances, the choline 2,6-xylyl ether

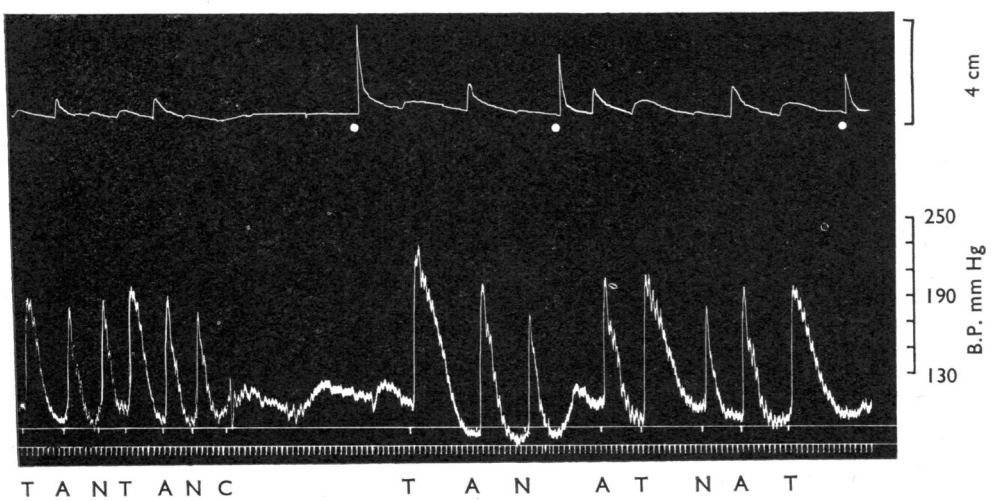

Fig. 1. The effect of choline 2,6-xylyl ether on the responses of the nictitating membrane (upper record) and the blood pressure (lower record) to the intravenous injection of various sympathomimetic amines in the cat anaesthetized with chloralose. The contractions of the nictitating membrane marked by white dots were obtained in response to supramaximal pre-ganglionic stimulation of the cervical sympathetic nerve and indicated the progress of the sympathetic nerve block produced by choline 2,6-xylyl ether. T=0.3 mg tyramine, A=5 μg adrenaline, N=3 μg noradrenaline, C=5 mg/kg choline 2,6-xylyl ether. Time in min.

produced a rapid block of the sympathetic nervous system; the pattern of potentiation of the effects of tyramine on the blood pressure and upon the nictitating membrane responses was unaltered. In two experiments, choline 2,6-xylyl ether failed to potentiate the effects of tyramine on the nictitating membrane.

In 4 of the 9 animals, doses of adrenaline and noradrenaline were given in addition to doses of tyramine. The effects of adrenaline on the blood pressure were always potentiated by choline 2,6-xylyl ether, whereas the nictitating membrane responses were unaffected, except in the experiment shown in Fig. 1. The blood pressure and nictitating membrane responses to noradrenaline were substantially unchanged.

In one experiment adrenalectomy did not alter the pattern of potentiation produced by choline 2,6-xylyl ether.

Spinal cats. Some of the observations of Burn & Rand on the effects of tyramine on the blood pressure and nictitating membrane were made in spinal cats. To make the present experiments more comparable with theirs and to eliminate compensatory mechanisms, the observations with choline 2,6-xylyl ether were repeated in spinal cats.

Five cats were used, and, after establishing regular pressor responses to tyramine, noradrenaline and adrenaline in each of these animals, three were given a dose of 5 mg/kg of choline 2,6-xylyl ether and two were given 10 mg/kg.

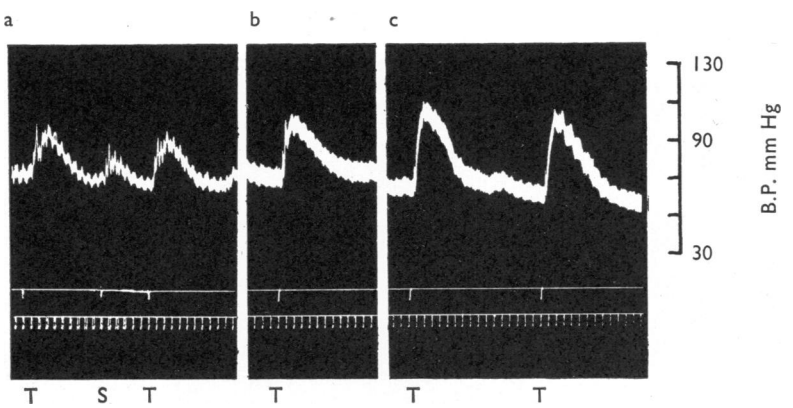

Fig. 2. Pressor responses to the intravenous injection of 0.3 mg of tyramine (T) in the spinal cat after chronic reserpine treatment. Record *a* shows control responses together with that to an equal volume of saline (S). Record *b* shows an increased response 37 min after the intravenous injection of 10 mg/kg of choline 2,6-xylyl ether. Record *c* shows a further increase in the responses 87 min after the injection of choline 2,6-xylyl ether. Time in min.

In all five animals the nictitating membrane responses to adrenaline and tyramine were potentiated, the effect reaching a maximum about 75 min after the injection of choline 2,6-xylyl ether. Subsequently, the responses began slowly to decline, but they were still considerably bigger than the control effects 2 hr after the dose of choline 2,6-xylyl ether. Prior to the injection of choline 2,6-xylyl ether, noradrenaline produced no contraction of the nictitating membrane in any of the experiments. It did produce a small response about 1 hr after the injection of the drug in two experiments.

In every experiment, the potentiation of the effect of tyramine on the nictitating membrane was much greater than the potentiation of the effect of adrenaline, and was considerably greater than it had been in the anaesthetized animals.

The effect of choline 2,6-xylyl ether on the pressor responses was inconsistent in spinal cats. It increased the duration of activity of the three drugs in all 5 animals, but increased the magnitude of the responses to adrenaline and tyramine in only 2 animals. One of these animals had been given 5 mg/kg and the other 10 mg/kg of choline 2,6-xylyl ether. The magnitude of the noradrenaline response was not increased in any of the animals. When the pressor responses were increased a picture was produced similar to that seen in anaesthetized cats and illustrated in Fig. 1. The effect differed from that seen in anaesthetized cats in that within 1 hr of injecting choline 2,6-xylyl ether the pressor responses to adrenaline and noradrenaline were smaller than their control effects, whilst that to tyramine remained potentiated. After 100 min the pressor response to tyramine was also smaller than the control.

Pretreatment with reserpine. Two cats were treated chronically with reserpine to deplete the tissue amines and were spinalized before recording the blood pressure responses to tyramine.

In these animals the pressor responses to doses of 0.3 mg of tyramine were very small. In one of them the immediate effect of a dose of 10 mg/kg of choline 2,6-xylyl ether was to abolish the response to tyramine and in the other it was reduced. However, tyramine began to produce pressor responses again after 25 min. Potentiation of the response began to occur about 40 min after the dose of choline 2,6-xylyl ether, and it continued to increase for one and a half hours (Fig. 2).

Pithed rats. The effect of an intravenous injection of 10 mg/kg of choline 2,6-xylyl ether on the response of the blood pressure to intravenous doses of tyramine and noradrenaline was determined in 4 atropinized-pithed rats. In all of these animals the responses to tyramine 5 to 30 μg were potentiated 10 to 15 min after giving

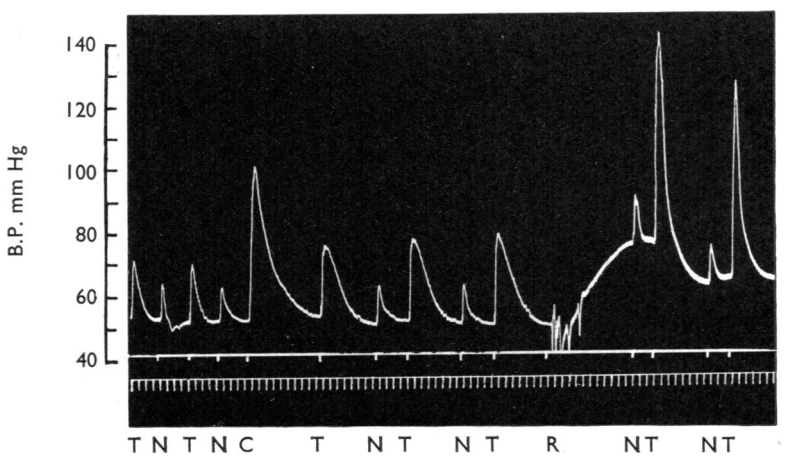

Fig. 3. The effect of choline 2,6-xylyl ether on pressor responses to intravenous injections of 5 μg tyramine (T) and 10 ng noradrenaline (N) in the atropinized-pithed rat. Ten min after the intravenous injection of 10 mg/kg of choline 2,6-xylyl ether at C the responses to tyramine were potentiated, whilst those to noradrenaline were unaffected. Reserpine 10 mg/kg was injected slowly intravenously at R, and 15 min later the response to tyramine was further potentiated while that to noradrenaline was slightly depressed. Time in min.

choline 2,6-xylyl ether. In 2 rats the response to 10 ng of noradrenaline was unchanged, in one it was potentiated slightly, and in another it was inhibited. The most frequently occurring result is illustrated in Fig. 3.

In 3 experiments, 10 mg/kg of reserpine was injected intravenously after the effects of choline 2,6-xylyl ether had been demonstrated. In these experiments the reserpine produced an immense potentiation of the effects of tyramine about 15 min after its injection. In two of the experiments the response to noradrenaline was unchanged, but in the third experiment it was depressed (Fig. 3).

This result suggested that the effect of an acute intravenous injection of reserpine in the absence of choline 2,6-xylyl ether might be of some interest. Accordingly, constant responses to intravenous doses of tyramine, noradrenaline and adrenaline

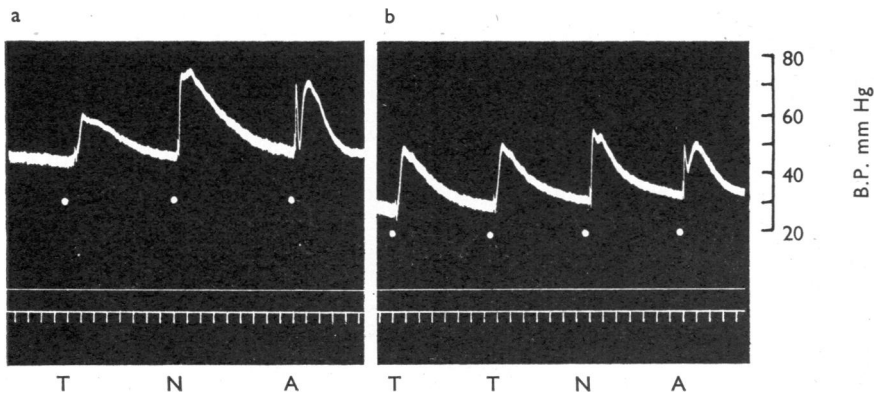

Fig. 4. Pressor responses to the intravenous injection of 10 μg tyramine (T), 3 ng noradrenaline (N), and 5 ng adrenaline (A) in the pithed-atropinized rat. Record *a* shows control responses to these drugs, and record *b* shows the responses to the same drugs 15 min after completing a slow intravenous injection of 10 mg/kg of reserpine. Time in min.

were established in 3 atropinized-pithed rats. Fifteen min after the injection of reserpine (10 mg/kg) the responses to tyramine were potentiated, whilst those to noradrenaline and adrenaline were slightly depressed (Fig. 4). The potentiation of the tyramine response in each of these animals was less than when the reserpine was given after choline 2,6-xylyl ether.

Interactions of sympathomimetic amines

Spinal cats. If the potentiation of the blood pressure response to tyramine produced by injecting reserpine acutely into the pithed rat was due to its releasing adrenaline or noradrenaline from the tissue stores, then there seemed to be two possible explanations of the mode of action. Either the reserpine facilitated the release by tyramine of a noradrenaline-like substance from the tissue stores, or the presence of noradrenaline in the extracellular fluid potentiated the action of tyramine.

To test the latter possibility constant pressor responses to suitable doses of tyramine, adrenaline and noradrenaline were established in 3 spinal cats. Noradrenaline was then infused at a rate of 10 μg/min. When doses of these three

drugs were injected during this infusion, and about 10 min after it was begun, the pressor responses to tyramine were potentiated whilst those to noradrenaline and adrenaline were slightly depressed. Doubling the infusion rate further increased the response to tyramine, whilst the responses to noradrenaline were further depressed. When the infusion was stopped the blood pressure immediately fell and the response to tyramine quickly returned to its pre-infusion magnitude, but the response to adrenaline and noradrenaline remained depressed (Fig. 5).

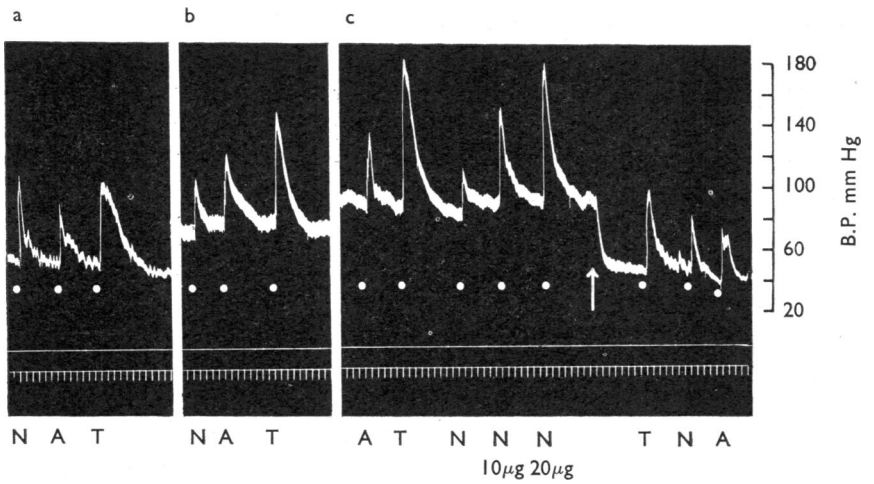

Fig. 5. The effect of infusing noradrenaline on the pressor responses to intravenous injections of 3 μg noradrenaline (N), 5 μg of adrenaline (A), and 0.3 mg tyramine (T) in the spinal cat. Record *a* shows control responses, record *b* shows responses obtained 10 min after the commencement and during the continued infusion of 2.8 μg/kg/min of noradrenaline; the response to tyramine was potentiated, to adrenaline slightly so and to noradrenaline was depressed. Record *c* shows the effects of raising the infusion rate to 5.7 μg/kg/min. The response to adrenaline remained unaltered, that to tyramine was further potentiated and to noradrenaline was further depressed. The infusion of noradrenaline was stopped at the arrow and the response to the three amines quickly returned towards normal. Time in min on lowest trace.

In one experiment isoprenaline was infused at the rate of 4 μg/kg/min. The pressor responses to the intravenous injection of tyramine and noradrenaline were depressed, whilst the response to adrenaline was increased. This result was recorded 30 min after the infusion of isoprenaline began. After 1 hr the infusion was stopped, and within 5 min the responses to tyramine, adrenaline and noradrenaline were all potentiated. At this point an infusion of 0.25 μg/kg/min of isoprenaline was begun and the response to tyramine was unchanged whilst the responses to noradrenaline and adrenaline were further potentiated. Thirty min after the commencement of this lower rate of infusion of isoprenaline, the tyramine response was much reduced, but that to noradrenaline was further increased (Fig. 6).

Pithed rats. Constant responses to doses of adrenaline, noradrenaline and tyramine were established in 3 pithed rats. When these doses were repeated during the infusion of 5 μg/kg/min of noradrenaline the response to tyramine was potentiated, that to noradrenaline was considerably depressed, and that to adrenaline

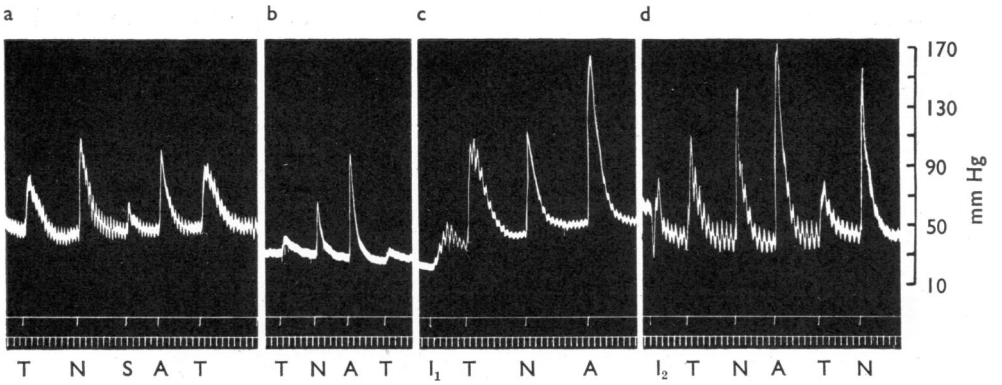

Fig. 6. The effect of infusing isoprenaline on the pressor responses to intravenous injection of 0.3 mg tyramine (T), 3.0 μg noradrenaline (N) and 10 μg adrenaline (A) in the spinal cat. Record *a*: control responses (S=saline). Record *b* was taken 30 min after commencement and during the continued infusion of 4 μg/kg/min of isoprenaline which depressed the response to tyramine and noradrenaline and potentiated the responses to adrenaline. In record *c* the infusion of isoprenaline was stopped at I_1 and the responses to the three amines were then potentiated. In record *d* an infusion of 0.25 μg/kg/min of isoprenaline was begun at I_2. This further potentiated the responses to noradrenaline and adrenaline, but depressed those to tyramine. Time in min.

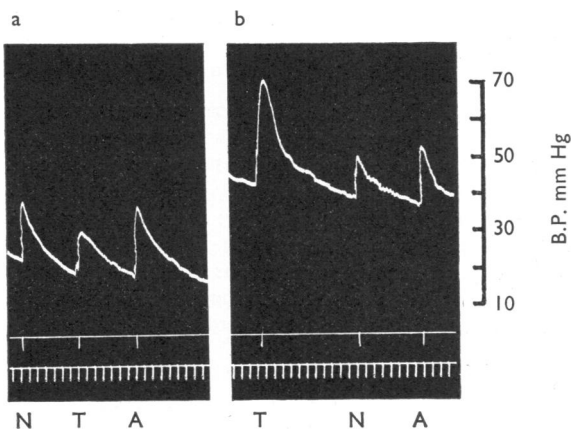

Fig. 7. Pressor responses to the intravenous injection of 20 ng noradrenaline (N), 20 μg tyramine (T), and 25 ng adrenaline (A) in the pithed-atropinized rat. Record *a*: control responses. Record *b* was taken 20 min after commencement and during the continued infusion of 5 μg/kg/min of noradrenaline which caused potentiation of the tyramine response and depression of the responses to noradrenaline and adrenaline.

slightly depressed (Fig. 7). Thus the pattern of the response to these drugs during the infusion of noradrenaline in the pithed rat was very similar to that in the spinal cat.

DISCUSSION

There is good evidence that tyramine can liberate catechol amines from tissue stores, and that many of its effects may be explained by supposing that this is the

mechanism of its action. The results obtained in the present series of experiments are difficult to reconcile with the view that the whole of the action of tyramine can be explained in this way. For example, in the presence of choline 2,6-xylyl ether, the effects of tyramine and adrenaline on the blood pressure and on the nictitating membrane of the anaesthetized cat are potentiated, whereas those of noradrenaline are not. Similar observations were made in spinal cats and on the pressor effects of these amines in pithed rats. Though the pressor effects in spinal cats were less consistent than they were in anaesthetized animals, the results imply either that the released amine is adrenaline, or that under the influence of choline 2,6-xylyl ether more noradrenaline is released by tyramine. The latter explanation is unlikely, because choline 2,6-xylyl ether still potentiates the action of tyramine in the spinal cat whose tissue noradrenaline stores have been depleted with reserpine. That the released amine is adrenaline is not precluded by these experiments, and the possibility would be in accord with the observations of Lockett & Eakins (1960b). However, during the infusion of isoprenaline in a spinal cat the pressor response to adrenaline was potentiated whilst the responses to tyramine and noradrenaline were depressed. This observation is not in harmony with the view that tyramine is effective by releasing adrenaline. It is unlikely that choline 2,6-xylyl ether potentiates the action of tyramine by releasing noradrenaline, and so adding to the effect of tyramine in this respect, because it does not affect noradrenaline responses. Furthermore, neither Exley (1957) nor Nasmyth & Andrews (1959) found any significant increase in plasma pressor amines after injections of choline 2,6-xylyl ether. Huković (1960) also concluded that choline 2,6-xylyl ether does not affect the tissue stores of catechol amines. Vane (1960) has shown that tyramine can combine with tryptamine receptors. It is possible, therefore, that choline 2,6-xylyl ether potentiates the effect of tyramine by affecting this combination. However, it also potentiates the action of adrenaline and there is no evidence that the latter drug can combine with tryptamine receptors.

Strong circumstantial evidence for the view that the response to tyramine is mediated by the release of noradrenaline was provided by the observations of Burn & Rand (1958a and 1960) that an infusion of noradrenaline or its precursors would restore the diminished pressor activity of tyramine in the spinal cat whose tissue catechol amines had been depleted by chronic reserpine treatment. This led them to suggest that the catechol amines replenished the tissue stores of noradrenaline, thus increasing the potential for release. Against this idea is the observation of Muscholl (1960) that reserpine prevents the uptake of noradrenaline by the rat heart. On the other hand, Pennefather & Rand (1960) showed that the uptake of noradrenaline by cat kidney and uterus was not prevented by reserpine. The experiments reported here demonstrate that an infusion of noradrenaline will potentiate the pressor actions of tyramine and depress those of adrenaline and noradrenaline in spinal cats or pithed rats. Furthermore, these effects occur during the continued infusion of large quantities of noradrenaline which might be expected to establish a diffusion gradient into the cell rather than out of it. It is clear that noradrenaline exercises a considerable influence over the activity of tyramine. Since the acute intravenous injection of reserpine produced results similar to those seen during the infusion of noradrenaline, it is not unreasonable to suppose that they

are due to the same thing; namely, to an elevation of the plasma noradrenaline level. Muscholl & Vogt (1957) have shown in rabbits that the maximal increase in the plasma adrenaline occurred between 30 and 40 min after giving reserpine. Thus the results obtained 15 min after the intravenous injection of reserpine could have been due to the elevation of the plasma catechol amine level by the drug. Schmitt & Schmitt (1960) reported that in the anaesthetized cat or dog the pressor effects of eighteen different sympathomimetic amines were potentiated 1 to 4 hr after the intraperitoneal injection of reserpine. These amines included tyramine, adrenaline and noradrenaline. The fact that the effects of adrenaline and noradrenaline were potentiated in their experiments and not in the experiments reported here is probably due to the difference in the interval between injecting reserpine and observing its effects on sympathomimetic amine responses. In the experiments of Schmitt & Schmitt it is probable that the release of catechol amines by reserpine was beginning to decline, whereas in the experiments described here the release would be reaching a peak.

There is incontrovertible evidence that tyramine is capable of releasing sympathomimetic amines from tissues associated with the sympathetic nervous system. However, the results obtained in the experiments described here do not seem to be compatible with the view that the whole of its sympathomimetic effects can be interpreted in terms of this release.

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