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THE VASODEPRESSOR ACTION OF NORADRENALINE

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In their classical study of the relation between chemical structure of amines and their sympathomimetic actions, Barger and Dale (1910) noted that a dose of ergotoxine sufficient to reverse the pressor effect of *dl*-adrenaline in the spinal cat did not reverse that of *dl*-noradrenaline. The pressor response of the latter substance was greater than that of the former, but relaxation of the isolated non-pregnant uterus was slight. Since that time many workers (Tainter, 1931; Greer, Pinkston, Baxter, and Brannon, 1937, 1938; Gaddum and Goodwin, 1947) have confirmed these findings, and found that yohimbine and most ergot alkaloids in addition to ergotoxine depress but do not reverse the pressor response to noradrenaline. Naturally occurring *l*-adrenaline and synthetic *dl*-noradrenaline were used for purposes of comparison. On some occasions, however, the action of noradrenaline was wholly inhibited or even slightly reversed by ergotamine, though never to the same extent as that of adrenaline (Stehle and Ellsworth, 1937). Melville (1937) showed that certain dioxane derivatives such as 933F and 883F failed to reverse the pressor action of noradrenaline but did reverse that of adrenaline. Dibenamine (Nickerson and Goodman, 1947) has also been used as an adrenaline antagonist.

The difference in response of similar doses of the two amines on the blood pressure of cats and dogs after the administration of an antagonist has been used (*a*) to support the theory that the substance liberated on stimulation of the hepatic nerves is noradrenaline or some similar substance (for references see West, 1947b), and (*b*) to confirm the observation that extracts of various mammalian organs (except placenta) contain a pressor substance with properties like those of noradrenaline (Euler, 1946). It has now been possible to demonstrate the vasodepressor action of noradrenaline in the cat by using large doses. The successful resolution of arterenol (*dl*-noradrenaline) by Tainter, Tullar, and Luduena (1948) has enabled this work to be completed with both *dl*- and *l*-noradrenaline.

METHODS

In different experiments, spinal cats, cats anaesthetized with chloralose or urethane, and rabbits anaesthetized with urethane were used. Blood pressure records were taken from the carotid artery; injections of the drugs were made into the femoral, jugular, or splenic veins, or into the external iliac artery so that the injected solution passed into the vessels of the opposite leg. In some cats, injections were also made into one of the two main splenic arteries. Movements of the duodenum and uterus were recorded directly. The adrenaline antagonists used were ergotoxine (5 mg./kg.), ergotamine tartrate (2 mg./kg.), and dibenamine (15 mg./kg.). For enhancement of the responses, cocaine hydrochloride (8 mg./kg.) was given intravenously.

In one experiment, samples of heparinized blood were taken from the femoral artery, and after being rapidly cooled were subjected to biological analyses (West, 1947b). Dialysed samples were tested on the perfused blood vessels of the frog (West, 1947a), whilst undialysed plasma samples were tested on the isolated uterus and ileum of the rat (de Jalon, Bayo, and de Jalon, 1945). Solutions of *l*-adrenaline, *dl*- and *l*-noradrenaline were prepared from the pure substances, which were kindly supplied by Dr. M. L. Tainter.

RESULTS

During the comparison of the pressor actions of adrenaline and *dl*-noradrenaline in the cat, it was confirmed that ergotoxine and ergotamine antagonized the vasopressor action of adrenaline, so that the vasodilator component was unmasked. No typical reversal occurred with noradrenaline since it has little vasodilator activity in comparable doses. When, however, the dose of noradrenaline was considerably increased (to more than twenty times the corresponding reversal dose of adrenaline), the vasodepressor action of noradrenaline became apparent (Fig. 1). After double vagotomy, the fall of blood pressure following the injection of 250 μg. noradrenaline into the femoral vein was still present. Intravenous atropine likewise was without effect on this response. It is worthy of note that the fall of blood pressure was prolonged, in contrast to

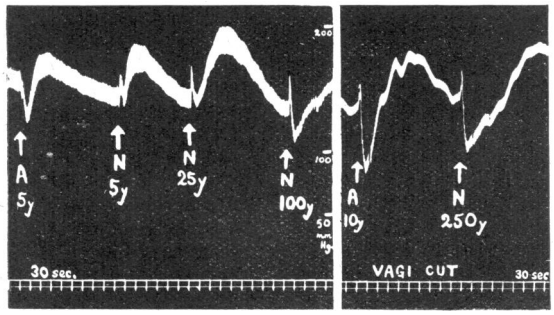

FIG. 1.—Cat 2.5 kg. Chloralose. Ergotoxine. The effect on the blood pressure of doses of *l*-adrenaline (A) and *dl*-noradrenaline (N) before and after vagotomy. All injections into the femoral vein.

the large transient fall after the administration of adrenaline, and never reached the maximum depression shown by doses of adrenaline. These two facts suggest a definite difference in the mode of production of the vasodepressor action.

In cats under chloralose receiving cocaine and ergotamine intravenously, similar reversals occurred, and in addition relatively small doses of noradrenaline produced falls of blood pressure. In one animal which had a steady blood pressure of about 200 mm. Hg throughout the whole experiment, 10 μg. of adrenaline by jugular vein produced maximal vasodilatation, whereas 250 μg. of noradrenaline exerted the maximal effect for this drug. These results were independent of the anaesthetic, since comparable results were obtained in spinal cats and in cats under urethane and chloralose. In a spinal cat, given cocaine and ergotoxine, the vasodepressor action of large doses of noradrenaline was only shown when the blood pressure had been raised to about 100 mm. Hg. As with the adrenaline vasodilatation, there is a limit to the amount of vasodepression obtainable by these drugs.

In a cat under urethane (Fig. 2), 30 μg. *dl*-noradrenaline after dibenamine produced a fall of blood pressure and relaxation of the ileum *in vivo* comparable with that produced by 1 μg. adrenaline. In this experiment, samples of heparinized blood were taken from the femoral artery before the administration of noradrenaline and at the peak of the fall of blood pressure after its administration. Half the number of samples were cooled immediately, centrifuged, and the plasma tested on the isolated uterus and ileum of the rat; the other half were cooled immediately, dialysed against $N/100$ HCl containing 0.1 g. glycine per 100 ml., and the dialysate tested on the perfused blood vessels of the frog. The results of the assays were calculated as noradrenaline and as adrenaline, and indicated that noradrenaline could be detected in the blood in

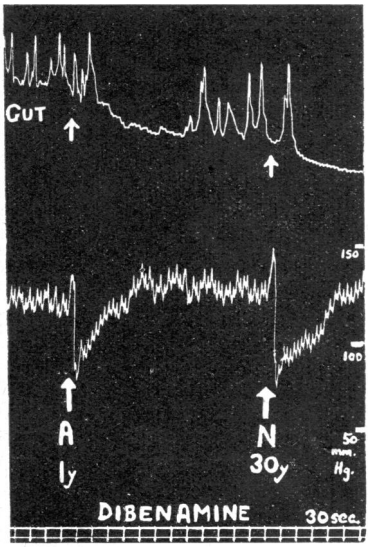

FIG. 2.—Cat 2.0 kg. Urethane. Dibenamine. Relaxation of the gut and fall in blood pressure produced by 1 μg. adrenaline (A) and 30 μg. noradrenaline (N) intrafemorally.

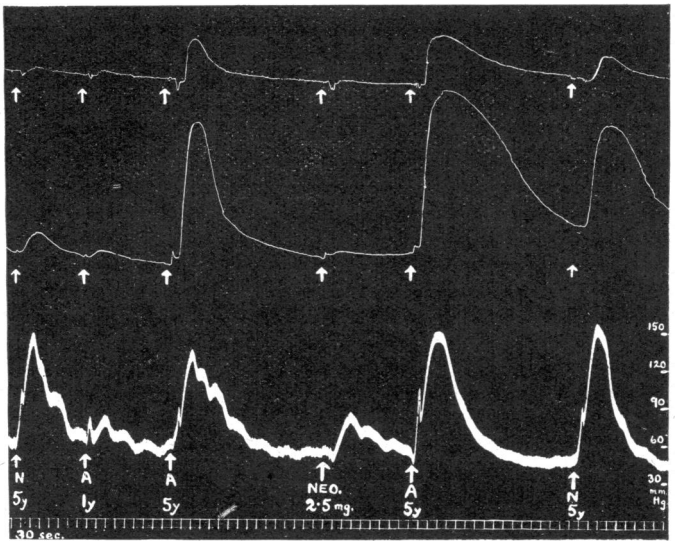

FIG. 3.—Cat 2.5 kg. Chloralose. Top record, right nictitating membrane; middle, left denervated nictitating membrane; bottom, blood pressure. Potentiation of the *l*-adrenaline (A) and *dl*-noradrenaline (N) response by the intravenous injection of 2.5 mg. neoantergan (Neo).

a concentration of 1.0–1.5 μg./ml. after the intravenous administration of 30 μg. It is possible that a small quantity of noradrenaline may be methylated, and that the subsequent fall of blood pressure may be due to adrenaline; this large dose of noradrenaline, on the other hand, may liberate small amounts of adrenaline from other tissues. The tests on the samples of blood indicated, however, that most of the noradrenaline was present as such; adrenaline (0.23–0.50 μg./ml.) was detected in the blood before the injections of the amines.

Effect of antihistamine substances on the vasodepressor response

It is well known that the motor actions of adrenaline are potentiated by antihistamine substances, presumably by antagonism of the histamine liberated during the adrenaline response. It seemed of interest, therefore, to determine the effect of antihistamine substances on the noradrenaline response, before and after ergotoxine or dibenamine. Neoantergan intravenously (1 mg./kg.) potentiated both the *l*-adrenaline and the *dl*-noradrenaline actions on the blood pressure and nictitating membranes (one denervated) of a cat under chloralose (Fig. 3). Benadryl and antistine in suitable doses potentiated these actions in a similar manner. After ergotoxine, however, the depressor responses to 5 μg. adrenaline and 100 μg. noradrenaline were unaffected. This indicates that the vasodepressor response to large doses of noradrenaline after ergotoxine or dibenamine is not due to a liberation of histamine.

Reversal of the vasodepressor response

Recently Neil, Redwood, and Schweitzer (1948) reported that the depressor response to aortic or sinus nerve stimulation in cats under pentobarbitone was converted into a rise of blood pressure by the intravenous injection of chloralose. The exact mechanism by which this change occurred was not determined. Small amounts of pentobarbitone were therefore administered to cats under chloralose. In Fig. 4, cocaine and dibenamine were first given intravenously, followed by vagotomy and neoantergan administration. Doses of 1 μg. adrenaline and 30 μg. noradrenaline produced the typical falls in blood pressure and relaxation of the non-pregnant uterus. Pentobarbitone (7 mg.) was then given and the cat was left for one hour. After this time, the vasodepressor response to large doses of noradrenaline was converted to a rise of blood pressure. The normal reversed action of adrenaline was unaffected, as also was the response to small doses of *iso*propyl-noradrenaline (Fig. 4, Is). After some time spontaneous reversion of the pressor to the depressor response with noradrenaline occurred. In order to exclude the possible effects of altered pulmonary ventilation on the blood pressure, this experiment was repeated with similar results under artificial respiration with bilateral open pneumothorax.

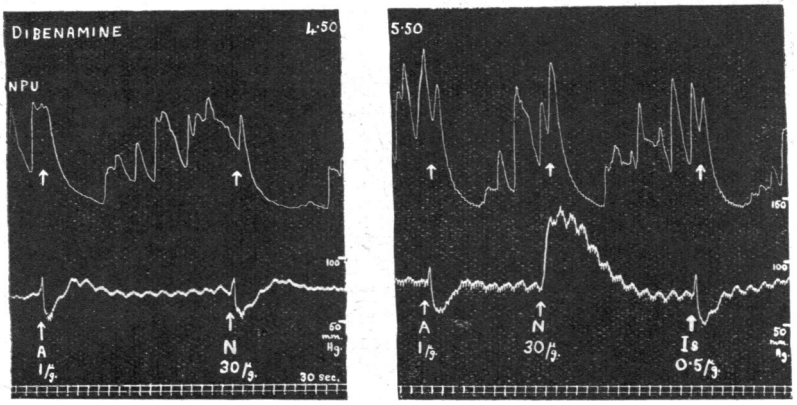

FIG. 4.—Cat 1.8 kg. Chloralose. Dibenamine and cocaine. Vagi cut. Neoantergan 1 mg./kg. intravenously. Relaxation of the non-pregnant uterus and fall in blood pressure produced by intrajugular doses of adrenaline (A) and noradrenaline (N). Between the left and right records, a period of one hour during which time 7 mg. pentobarbitone were given intravenously. Note the reversal of the noradrenaline action on the blood pressure but not that of adrenaline. The response to 0.5 μg. *iso*propyl-noradrenaline (Is) was also unaffected.

Injections by other routes

The more active *l*-noradrenaline was used for these experiments. In cats under chloralose, it was confirmed that the ratio of equipressor doses of *l*-noradrenaline and *l*-adrenaline was about 0.6 (Tainter, Tullar, and Luduena, 1948; Graham, 1949). After the ergot alkaloids or dibenamine, both substances exhibited depressor responses by the femoral, jugular, and intraportal routes, but the ratio of doses producing maximal vasodepression was reduced from 30:1 (Fig. 2) to 8:1 (Fig. 5, FV) for the femoral route. When injected into the artery supplying the caudal end of the spleen of cats without ergot or dibenamine, noradrenaline produced pure rises of blood pressure at all dose levels, whereas adrenaline injections gave small rises of pressure followed by large falls. After dibenamine, similar injections of both drugs produced depressor responses, that of noradrenaline being much less marked than that of

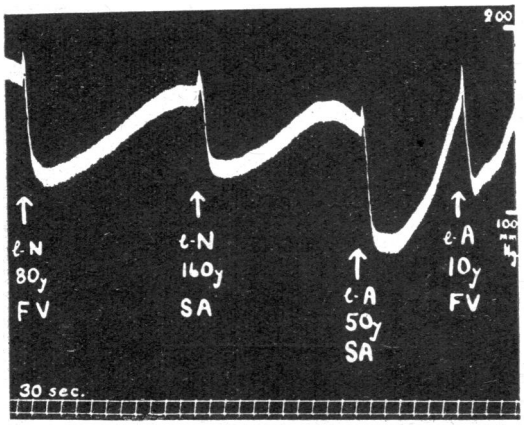

FIG. 5.—Cat 3.2 kg. Chloralose. Ergotoxine. The effect on the blood pressure of doses of *l*-adrenaline (A) and *l*-noradrenaline (N) injected into the splenic artery (SA) and the femoral vein (FV).

adrenaline (Fig. 5, SA). These effects were independent of the anaesthetic, since comparable results were obtained in cats under urethane or ether. As reported earlier (West, 1948), the latent period of noradrenaline injections by splenic artery was always longer than that of adrenaline.

When injected into the external iliac artery (so that the injected solution passed into the vessels of the opposite leg), 1 μg. adrenaline after cocaine and dibenamine was required to cause the same fall of blood pressure as 0.5 μg. adrenaline by jugular vein. When noradrenaline was injected in a similar manner, 15 μg. by the jugular vein produced a comparable fall of blood pressure, but all intra-arterial doses up to 100 μg. failed to elicit the true vasodepressor response. Further evidence that the vasodepressor responses of adrenaline and noradrenaline are the result of different mechanisms was shown by perfusion experiments. The hind limbs of cats were perfused with oxygenated Locke's solution at 37° C., and the outflows recorded in a drop-timer (Gaddum and Kwiatkowski, 1938). In this preparation, small doses of adrenaline caused vasodilatation after dibenamine (given slowly), whereas similar doses of noradrenaline were without effect. In addition, an increase in the dose of the latter had no vasodepressor action.

Experiments with rabbits

In a few rabbits, it was shown that the ratio of equi-pressor doses of *l*-noradrenaline and *l*-adrenaline was about 2.0, confirming previous observations (West, 1948) that adrenaline is more active than noradrenaline in this animal. After ergotoxine, pressor responses of both drugs were almost wholly reduced but not reversed. Cannon and Lyman (1913) reported that the rabbit, in contrast to the cat, appears to lack a sympathetic depressor component capable of being unmasked by blocking agents such as ergotoxine. Large doses of *l*-adrenaline and *l*-noradrenaline (up to 1 mg.) failed to elicit any depressor action. Similar results were found in rabbits after dibenamine, though it was difficult to administer this drug satisfactorily to these animals.

DISCUSSION

Previous workers have shown that a dose of a sympatholytic agent sufficient to reverse the pressor effect of adrenaline does not reverse that of noradrenaline. Equi-pressor doses of the two amines before the administration of the antagonist were used to demonstrate this difference in response. The observation that noradrenaline in suitable doses can produce regular vasodepressor responses in cats which have been treated with ergotoxine or dibenamine is important. The fall in blood pressure only occurs after large doses of noradrenaline; also it is always more prolonged than that produced by adrenaline, and never reaches such low levels. West (1948) showed that after large intraportal doses of dihydroergotamine in cats, it was sometimes possible to obtain depressor responses to small intraportal doses of noradrenaline, when similar doses of adrenaline were without effect. Nickerson and Goodman (1947) reported that the reversal of the adrenergic vasopressor effect by dibenamine was not altered by atropine, benadryl, and pyribenzamine, or by the anaesthetic used, and was due to vasodilatation.

The mechanism by which the vasodepressor response to noradrenaline is produced is not clear. Several possibilities exist: (1) Constriction of the coronary arteries may occur. Bacq and Fischer (1947) reported that extracts of human coronary nerves and arteries contain adrenaline, and they suggested that in certain diseases the synthesis of adrenaline is stopped at the stage of noradrenaline, which may have a vasoconstrictor action on the coronary vessels. In direct contrast to this suggestion, Marsh, Pelletier, and Ross (1948) showed that noradrenaline increased cardiac output and coronary flow in isolated mammalian hearts. (2) Constriction of branches of the portal vein in the liver may be produced. In two cats given dibenamine, the whole portal vein was closed, and when the blood pressure was stabilized large doses of noradrenaline still exhibited vasodepressor responses. (3) Constriction of the pulmonary arteries may take place. A rise in pressure in the pulmonary vessels has been shown to induce a fall in the systemic circulation in a cat (Parin, 1947); this fall was the result of a cardiac component and a circulatory component. The changes in the general circulation were due to vasodilatation, the spleen increasing in volume as long as its nerve supply remained intact. It was considered probable that pressoreceptor reflexes arise in the pulmonary artery, and it is possible that the depressor response to noradrenaline may be produced by this mechanism. In all the experiments with pentobarbitone, reversal to a pressor response did not occur immediately but was maximal after about an hour, when the vasodilator action of adrenaline still existed. It is not known whether excess of pentobarbitone affects the fall in systemic pressure induced by a rise in pressure in the pulmonary arteries.

Summary

1. Large doses of *l*- and *dl*-noradrenaline produced vasodepressor responses in cats given ergotoxine or dibenamine. No such action was noted in rabbits.

2. The mechanism by which this fall of blood pressure is produced has been studied. It is probably not due to vasodilatation, as is the normal adrenaline reversal response.

3. Intravenous injection of pentobarbitone converted the depressor response to a rise of blood pressure in cats under chloralose.

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