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THE DEPRESSOR ACTION OF DOPAMINE AND ADRENALINE

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Dopamine is a pressor agent in the spinal cat, but causes a fall of blood pressure in the guinea-pig and rabbit under urethane anaesthesia. When guinea-pigs and rabbits are injected with reserpine, which depletes the vessel walls of noradrenaline, dopamine then becomes pressor. If an intravenous infusion of noradrenaline is given the depressor action returns. An intravenous infusion of vasopressin does not have this effect.

A strip of rabbit aorta is caused to contract by noradrenaline and by dopamine, but if dopamine is added at the height of a noradrenaline contraction it causes relaxation.

Adrenaline causes a fall of blood pressure in the cat under ether with vagi cut. However, in a reserpine-treated cat its action is pressor. The depressor action is restored during an infusion of noradrenaline. Noradrenaline has thus been shown to cause a vasomotor reversal of dopamine and of adrenaline.

Dopamine, or 3-hydroxytyramine, belongs to the group of sympathomimetic amines which contains adrenaline and noradrenaline, all the members of this group being derivatives of catechol. When injected intravenously into the spinal cat dopamine has a pressor action. It was therefore a surprise that Holtz and Credner (1942) found that dopamine caused a fall of blood pressure in the guinea-pig and in the rabbit. Interest in this observation has been renewed by the work of Hornykiewicz (1958), who confirmed the results of Holtz and Credner (1942), and showed that the depressor action of dopamine in the guinea-pig was increased by the previous injection of iproniazid, which inhibits amine oxidase.

We have recently found that sympathomimetic amines such as tyramine and ephedrine depend for their action on the noradrenaline present in the walls of the arteries, and that when the noradrenaline is dispersed from the walls by the injection of reserpine, tyramine and ephedrine no longer cause a rise of blood pressure (Burn and Rand, 1958a and b). For reasons which will be discussed later we decided to examine the action of dopamine in guinea-pigs and rabbits treated with reserpine, to see if its depressor action was modified.

METHOD

Guinea-pigs were anaesthetized by injecting urethane intraperitoneally in a dose of 1.5 g./kg. Rabbits were anaesthetized by injecting urethane intravenously; the dose was variable, enough being given to abolish all reflexes. Reserpine was given intraperitoneally after dissolving it in 20% ascorbic acid, the total dose being about 10 mg./kg. for a guinea-pig, 6 mg./kg. for a rabbit, and 5 mg./kg. for a cat: this dose was usually divided and given on two days. Rabbits were decapitated by Sherrington's method and spinal cats were prepared by Dale's method.

RESULTS

Reversal of Dopamine Action in the Guinea-pig.—When dopamine was injected into a normal guinea-pig under urethane anaesthesia, it caused a fall of blood pressure as shown in Fig. 1*a*. This fall was proportional to the dose as was found by Hornykiewicz (1958). When the injection was made into a guinea-pig which had received reserpine on the previous day, there was a rise of blood pressure (Fig. 1*b*). The rise occurred when 80 μg. was injected as shown, or when 20 μg. was injected, being proportional to the dose.

We have already stated that in the reserpine-treated cat tyramine has no pressor action; we observed that the pressor effect was restored when an intravenous infusion of noradrenaline was given. We therefore gave an intravenous infusion of noradrenaline to the reserpine-treated guinea-pig, and, as shown in Fig. 1*c*, after 10 μg. of noradrenaline had been infused the injection of 80 μg. dopamine caused a fall of blood pressure.

Reversal of Dopamine Action in the Rabbit.—When dopamine was injected into a normal rabbit

under urethane anaesthesia it caused a fall of blood pressure in amounts from 0.1 to 0.4 mg., but when larger amounts were given a pressor phase was superimposed on the fall. Results in one rabbit are shown in Fig. 2*a*; when 0.8 mg. dopamine was injected the pressor phase was becoming evident. When the same injections were made in a rabbit previously treated with reserpine, the effect in every case was pressor as shown in Fig. 2*b*. Thus treatment with reserpine reversed the depressor action of dopamine in the rabbit as well as in the guinea-pig.

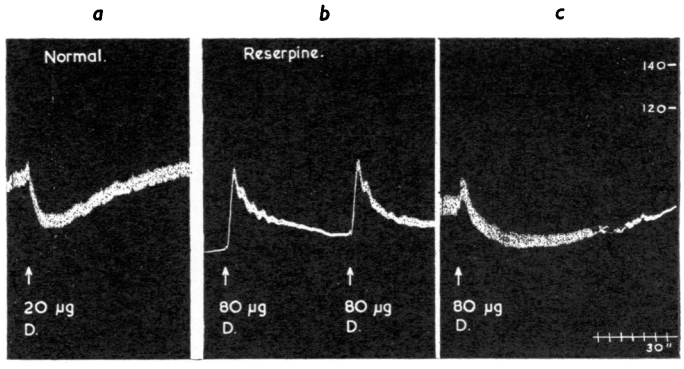

FIG. 1.—Guinea-pig blood pressure. (*a*) 20 µg. dopamine (D) given to normal guinea-pig i.v. (*b*) 80 µg. dopamine given to reserpine-treated guinea-pig. (*c*) 80 µg. dopamine injected after intravenous infusion of 10 µg. noradrenaline.

We took the opportunity to observe the action of isoprenaline on the blood pressure of the reserpine-treated rabbit. We saw that in one rabbit in which 0.1 mg. dopamine had a simple pressor action, the injection of 10 µg. isoprenaline caused a fall of blood pressure as in a normal animal. Similarly in the reserpine-treated guinea-pig isoprenaline in amounts of 0.2 and 2 µg. was depressor, though dopamine was pressor.

Conversion of Pressor to Depressor Effects.—The effects which we observed with dopamine were also observed with epinine, a substance in which the amine group of dopamine becomes methylamino. Epinine, while depressor in the normal rabbit in doses up to 0.2 mg., was pressor in the reserpine-treated rabbit as shown in Fig. 3*a*. When noradrenaline was given by slow intravenous infusion, the injection of 0.2 mg. epinine caused a fall of blood pressure (Fig. 3*b*). The infusion of noradrenaline was then stopped, and after a short time the pressor action of 0.2 mg. of epinine returned (Fig. 3*c*). An infusion of vasopressin (1 unit in 5 ml.) was then given, raising the blood pressure to the level during the infusion of noradrenaline. The injection of 0.2 mg. of epinine still caused a rise of pressure; its action was not reversed as during the infusion of noradrenaline. Similar observations were made with dopamine in reserpine-treated rabbits. Its pressor action persisted when it was injected during the infusion of vasopressin, but was reversed during an infusion of noradrenaline.

As already explained, when larger amounts of dopamine or of epinine were injected into normal

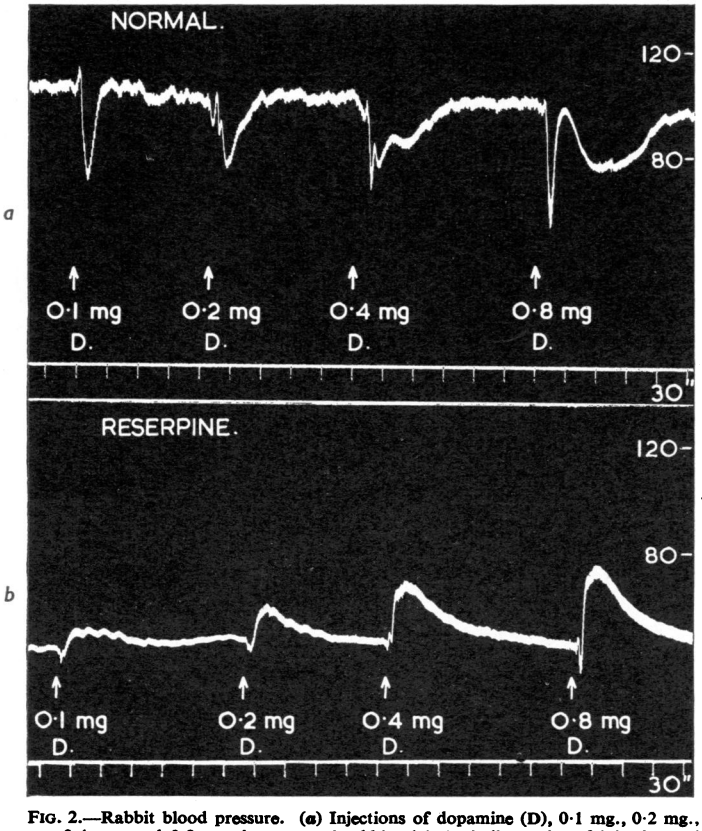

FIG. 2.—Rabbit blood pressure. (*a*) Injections of dopamine (D), 0·1 mg., 0·2 mg., 0·4 mg. and 0·8 mg. into normal rabbit. (*b*) A similar series of injections of dopamine into a rabbit treated with reserpine.

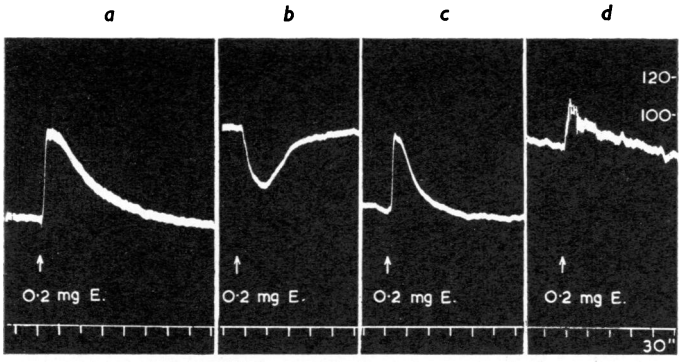

FIG. 3.—Blood pressure of rabbit treated with reserpine. (*a*) 0·2 mg. epinine (E). (*b*) 0·2 mg. epinine during infusion of noradrenaline. (*c*) 0·2 mg. epinine after infusion of noradrenaline. (*d*) 0·2 mg. epinine during infusion of vasopressin (1 unit in 5 ml.).

rabbits, a pressor response superimposed on the depressor action was recorded. This pressor response was caused to disappear by infusing noradrenaline. Thus in Fig. 4*a*, 1.6 mg. of dopamine caused a pressor effect in a normal rabbit. A noradrenaline infusion was then begun at a slow rate, the blood pressure not being very much raised. During the infusion the injection of 1.6 mg. of dopamine had the effect shown in Fig. 4*b*. When a total of 0.3 mg. of noradrenaline had been infused, the infusion was stopped. Over one hour later the injection of 1.6 mg. of dopamine had a simple depressor action. A similar result was obtained with epinine.

Dopamine in the Decapitate Rabbit.—The foregoing observations were made under urethane anaesthesia. We found that in a decapitate rabbit, although not previously treated with reserpine, the injection of dopamine had a pressor action as in the spinal cat. This pressor action, however, was abolished during the infusion of noradrenaline as shown in Fig. 5*a* and sometimes reversed to a depressor action. During the infusion of vasopressin, however, the pressor action of dopamine was sometimes greatly increased as shown in Fig. 5*b*.

Observations on Rabbit Aorta.—In order to reduce the number of factors concerned in changes in the blood pressure of the whole animal, we made observations on strips of rabbit aorta cut spirally and suspended in Locke solution in an 8 ml. bath. On each spiral we tested the effect of adding different amounts of noradrenaline to the bath and also of different amounts of dopamine. Both amines caused a contraction of the aorta. We also tested the effect of adding dopamine to the bath when noradrenaline had been added to the bath some minutes before and had produced a contraction which was sustained. In one experiment we observed that 16 μg. of noradrenaline caused a contraction of 67 mm. as recorded on the drum; after the bath fluid was changed and the aorta was fully relaxed, the addition of 10 mg. of dopamine caused a contraction of 55 mm. When, however, 10 mg. of dopamine was added at the height of the noradrenaline contraction, it caused a partial relaxation of the aorta. We then studied the effect of adding 10 mg. dopamine to the bath after the addition of different amounts of noradrenaline. When 2 μg. of noradrenaline had caused its maximal effect, 10 mg. of dopamine caused a further contraction. When 5 μg. of noradrenaline had caused its maximal effect, 10 mg. dopamine had little effect. When 16 μg. of noradrenaline had caused its maximal effect, 10 mg. of dopamine caused relaxation as shown in Fig. 6, and a further 10 mg. of dopamine caused a greater relaxation. We observed these changes in each of six experiments.

Reversal in the Cat.—The ordinary view that dopamine is a pressor amine like adrenaline depends on its action in the spinal cat. Its action in this preparation is indeed like that of adrenaline since it is reversed, and becomes mainly depressor after the injection of ergotamine, as shown in Fig. 7*a*. Because dopamine is pressor in the spinal cat its depressor action in the guinea-pig and the rabbit might be regarded as a species

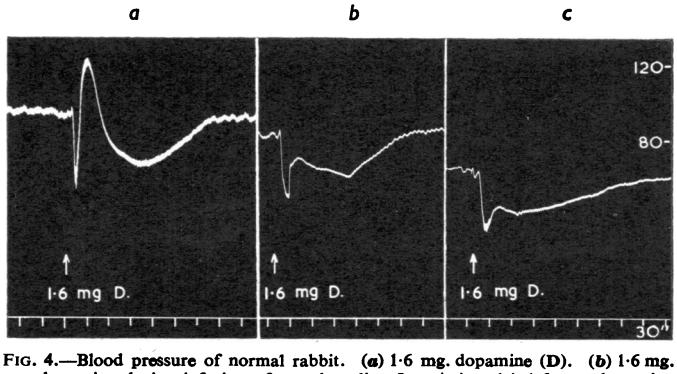

FIG. 4.—Blood pressure of normal rabbit. (*a*) 1·6 mg. dopamine (D). (*b*) 1·6 mg. dopamine during infusion of noradrenaline 5 μg./min. (*c*) 1·6 mg. dopamine given 77 min. after infusion of noradrenaline was stopped.

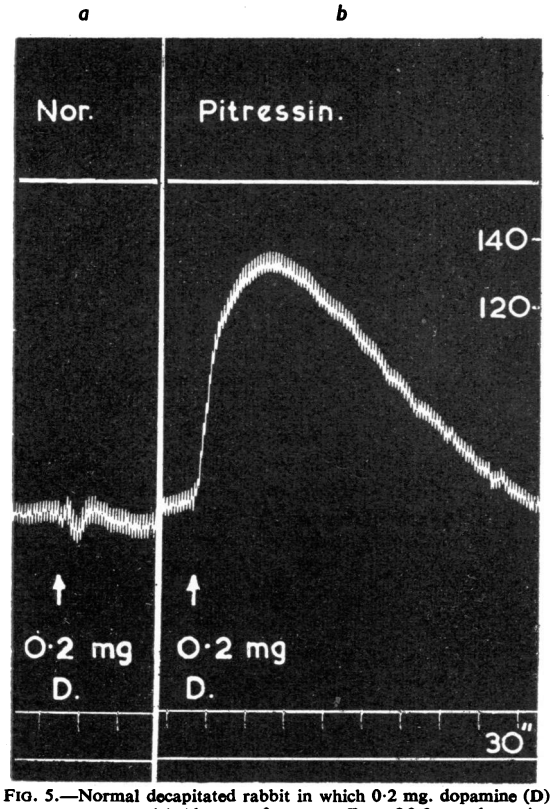

FIG. 5.—Normal decapitated rabbit in which 0·2 mg. dopamine (D) was pressor. (*a*) Absence of pressor effect of 0·2 mg. dopamine during noradrenaline infusion. (*b*) Greatly increased pressor effect of 0·2 mg. dopamine during infusion of vasopressin (Pitressin).

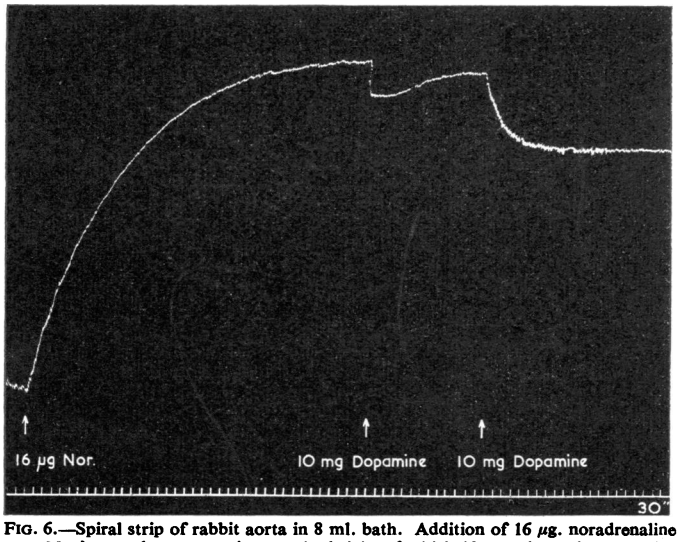

FIG. 6.—Spiral strip of rabbit aorta in 8 ml. bath. Addition of 16 µg. noradrenaline (Nor) caused a contraction, at the height of which 10 mg. dopamine caused a relaxation. The addition of another 10 mg. dopamine caused a further relaxation.

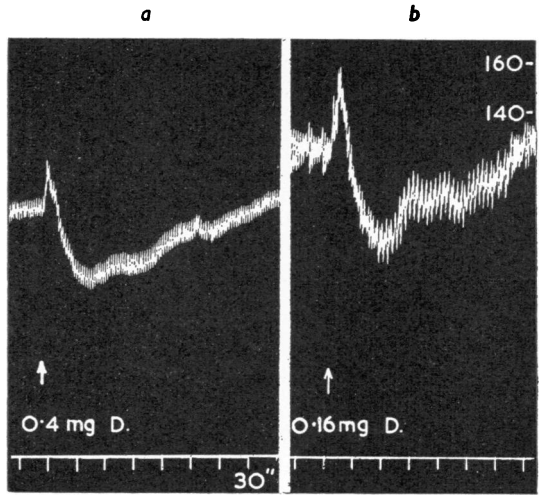

FIG. 7.—Cat blood pressure. (*a*) Spinal preparation after the injection of 2 mg. ergotamine; injection of 0·4 mg. dopamine (D) caused a fall of pressure. (*b*) Animal anaesthetized with urethane; injection of 0·16 mg. dopamine caused a fall in the blood pressure similar to that seen in (*a*).

difference. The difference seems to depend rather on the difference between the spinal preparation and the animal under urethane, for dopamine causes mainly a fall of pressure in the cat under urethane, and this fall resembles the fall of pressure in the spinal cat which has received ergotamine. Fig. 7*a* may be compared with Fig. 7*b*.

We have observed that the pressor action of dopamine in the spinal cat can be reversed to a depressor by a slow intravenous infusion of noradrenaline. In the experiment shown in Fig. 8, noradrenaline was infused for 38 min., the total infused being 3.23 mg. Before the infusion began 50 µg. dopamine had a pressor effect, and after the infusion 5 mg. dopamine caused a small but prolonged depressor effect. This was a large dose, but it is well known that the most marked depressor effect of adrenaline after ergotamine is seen when large doses such as 0.1 mg. are given, to which 5 mg. dopamine can be regarded as equivalent.

Depressor Action of Adrenaline.—Moore and Purinton (1900) described the depressor action of small doses of adrenaline in the anaesthetized cat. Dale and Richards (1918) showed that this fall was well seen in the cat anaesthetized with ether when the vagi were cut, and that it was attended

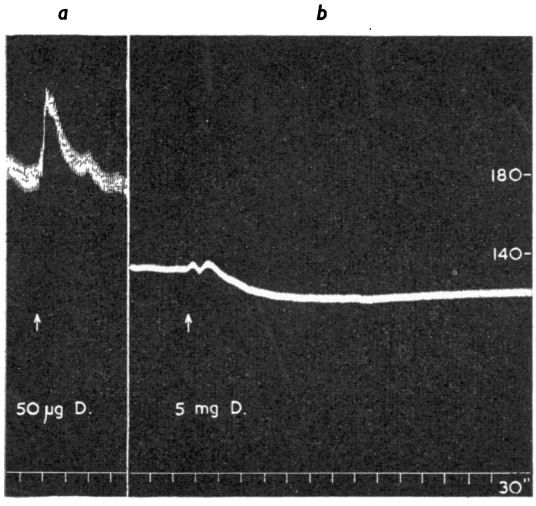

FIG. 8.—Blood pressure of spinal cat. (*a*) 50 µg. dopamine (D) caused a rise. An intravenous infusion of noradrenaline was then given during 35 min., the total being 3·23 mg. (*b*) After the end of the infusion, when the blood pressure was lower than in (*a*), the injection of 5 mg. dopamine caused a fall of blood pressure.

by dilatation of the hindleg in which the sciatic nerve had been cut some days previously. It seemed likely that the depressor action of dopamine would be evident under the same conditions. Fig. 9 shows a comparison of the effect of adrenaline with that of dopamine. The adrenaline was given by slow infusion from a burette during 2 min. Dopamine was given in the same way for a period of 80 sec., producing a much greater fall than was obtained with adrenaline.

In cats treated with reserpine, anaesthetized with ether and with the vagi cut, a slow intravenous infusion of adrenaline during 1 min. caused a rise of pressure (Fig. 10*a*). When a slow infusion of noradrenaline was given during 20 min. and during this period the infusion of adrenaline for 1 min. was repeated, there was a fall of pressure (Fig. 10*b*). After the infusion of noradrenaline was stopped and the blood pressure had fallen to a lower level than in Fig. 10*a*, the infusion of adrenaline now had only a slight pressor effect with a depressor component (Fig. 10*c*).

Observations were next made in cats in which the left sciatic nerve had been cut about 8 days previously. On the two days preceding the experiment the cats were injected with reserpine. They were then anaesthetized with ether, and the volume of the left hindleg was recorded by putting it in a plethysmograph, using a piston recorder. The vagi were cut. Adrenaline was then given intravenously, 5 µg. or 10 µg. being infused in 1 min. Whereas in a normal cat this would have caused a fall of blood pressure and dilatation of the hindleg, in reserpine-treated cats it caused a rise of blood pressure which was sometimes large and accompanied by constriction of the hindleg, but was usually small and without much change in leg volume as shown in Fig. 11 (*a*) and (*b*). A slow infusion of noradrenaline was then given during a period of 15 min. During this time when the blood pressure was not greatly raised, the slow infusion of 10 µg. and 5 µg. of adrenaline in 1 min. was repeated. It now caused a fall in blood pressure and dilatation of the leg as shown in Fig. 11 (*c*) and (*d*).

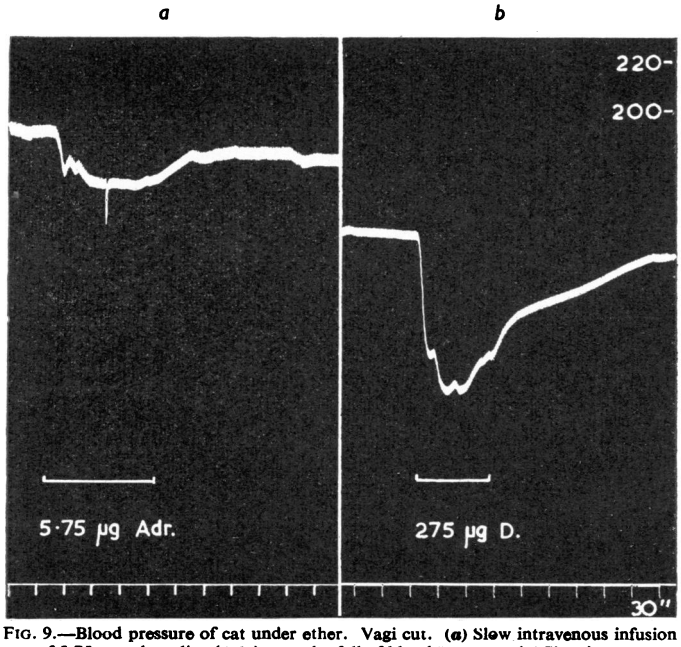

FIG. 9.—Blood pressure of cat under ether. Vagi cut. (*a*) Slow intravenous infusion of 5·75 µg. adrenaline (Adr) caused a fall of blood pressure. (*b*) Slow intravenous infusion of 275 µg. dopamine (D) caused a much larger fall of blood pressure.

Noradrenaline Stored in the Walls.—We extracted the aortae of eight cats to determine the amount of noradrenaline present. Four were cats under urethane and four were converted to spinal cats. We found no difference in the mean figure for noradrenaline in the two groups. The cats under urethane contained 0.295 µg./g. aorta, while the spinal cats contained 0.265 µg./g.

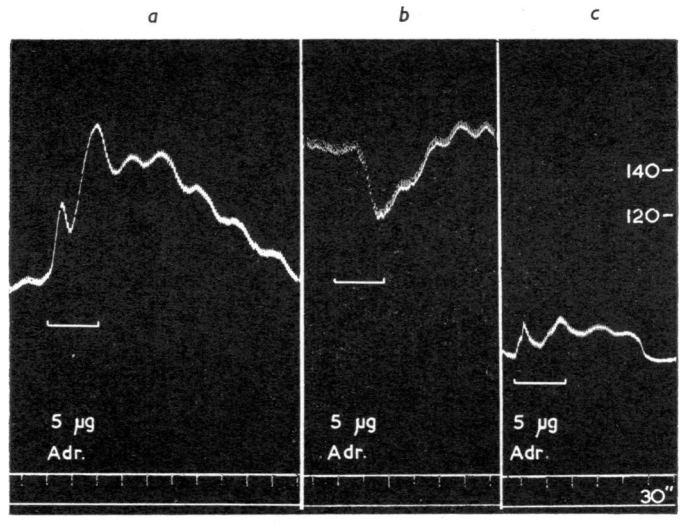

FIG. 10.—Blood pressure of cat treated with reserpine. Ether anaesthesia. Vagi cut. (*a*) Intravenous infusion of 5 µg. adrenaline (Adr) during 1 min. caused a rise of pressure. (*b*) During an infusion of noradrenaline which was given for 20 min., an infusion of 5 µg. adrenaline during 1 min. caused a fall of pressure. (*c*) After the infusion of noradrenaline was stopped, and the blood pressure had fallen below the level in (*a*), the infusion of 5 µg. adrenaline during 1 min. caused a much smaller pressor effect than in (*a*), and this effect had a depressor component.

Pressor Ratios of Noradrenaline, Adrenaline, and Dopamine.—We have shown (Burn and Rand, 1958b) that the pressor action of noradrenaline and other catechol amines is much increased in the spinal preparation of a cat which has been treated with reserpine, and that it is decreased after an intravenous infusion of noradrenaline. We compared the pressor activity of noradrenaline, of adrenaline, and of dopamine in two cats treated with reserpine; we found that in one the pressor action of adrenaline was 1/4 of that of noradrenaline, while that of dopamine was 1/100th of that of noradrenaline. In the other the action of adrenaline was 1/8 of that of noradrenaline, while that of dopamine was 1/150th of that of noradrenaline. These figures are different from those obtained using the spinal preparation of normal cats. Barger and Dale (1910) found the potency of adrenaline to be 2/3 or 4/5 of that of noradrenaline, while Gurd (1937) found the potency of dopamine to be about 1/30th of that of adrenaline.

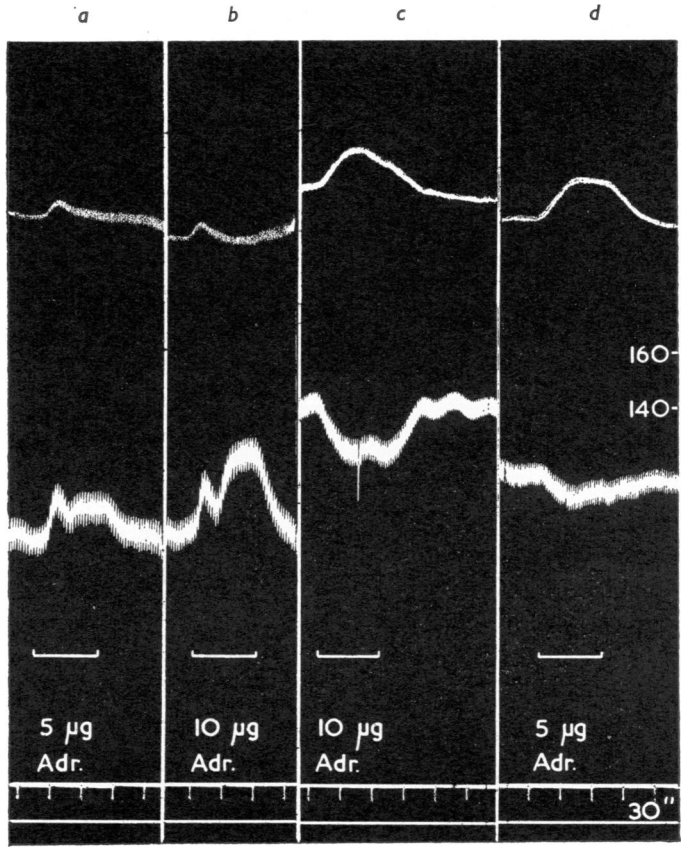

FIG. 11.—Cat with left sciatic nerve cut 8 days. Treated with reserpine. Ether anaesthesia, vagi cut. Upper record: volume of left hindleg. Lower record: blood pressure. (*a*) Infusion of 5 µg. adrenaline (Adr). (*b*) Infusion of 10 µg. adrenaline. A slow infusion of noradrenaline was then given. During this infusion (*c*) an infusion of 10 µg. adrenaline was also given, and (*d*) an infusion of 5 µg. adrenaline was also given. Note the pressor effect in (*a*) and in (*b*) accompanied by little change of leg volume. Note the depressor effect in (*c*) and (*d*) accompanied by dilatation of leg volume.

Discussion

When we first considered the depressor action of dopamine in the guinea-pig and in the rabbit, we had the idea that it might be related to the presence of noradrenaline in the vessel walls, both that which was liberated at sympathetic nerve endings and also that which was stored in the walls (Schmiterlöw, 1948). Dopamine is a much weaker constrictor agent than noradrenaline, its pressor action in the reserpine-treated spinal cat being only 1/100th or 1/150th of that of noradrenaline. We thought that an injection of dopamine into the normal guinea-pig or rabbit under urethane would set up competition between dopamine and noradrenaline for receptor sites. Dopamine would replace noradrenaline for some of these sites, but, being a much feebler constrictor agent, its occupation of these sites would result in a fall of vascular tone. We decided to test this view by treating animals with reserpine.

When an animal is treated with reserpine there is a diminution of sympathetic tone (Bein, 1955) and there is a disappearance of noradrenaline from the vessel walls (Burn and Rand, 1957). Consequently in the reserpine-treated guinea-pig and rabbit, dopamine when injected would find fewer receptor sites in the vessel wall occupied by noradrenaline, and would therefore produce a rise of blood pressure by occupying those which were free. This is what it was found to do.

The pressor action in the spinal cat of sympathomimetic amines like tyramine is absent if the cat is previously treated with reserpine, but it returns after an intravenous infusion of noradrenaline. Presumably this indicates that the intravenous infusion of noradrenaline replenishes stores of noradrenaline in the artery wall which are depleted by treatment with reserpine. If from the replenished store in the wall there is a small discharge of noradrenaline which occupies some of the receptor sites, then after an infusion of noradrenaline the injection of dopamine would again lead to competition between dopamine and noradrenaline for the receptor sites, and would produce a fall of blood pressure. It was in fact found that after an infusion of noradrenaline into the reserpine-treated guinea-pig and rabbit, dopamine once more had a depressor action.

That the effect of the infusion of noradrenaline was not due to a mere rise in vascular tone was evident from the observation that when an infusion of vasopressin was given which raised the blood pressure to the same extent, dopamine still exerted a pressor action. This observation was made in each of a series of experiments, and in one the pressor action of dopamine was greatly increased during infusion of vasopressin.

The depressor action of dopamine in the guinea-pig and rabbit under urethane has attracted attention because it stands in contrast to the pressor action seen in the spinal cat. The difference is, however, not due to the species, because dopamine is mainly depressor in the cat under urethane, and because it is pressor in the decapitate rabbit. The difference between the response of the cat under urethane and that of the spinal cat must be due to the noradrenaline which is liberated at sympathetic nerve endings to maintain tone. It was not due to a difference in the amount of noradrenaline stored in the artery wall, for no difference was found. However, when an infusion of noradrenaline was made into the spinal cat or into the decapitate rabbit, the pressor action of dopamine was first abolished and then reversed.

Observations on isolated strips of rabbit aorta have been in accord with this explanation of the pressor and depressor actions of dopamine. Both noradrenaline and dopamine were found to cause contractions of such strips; these contractions were similar in height when the dose of noradrenaline (in an 8 ml. bath) was 16 μg., and when the dose of dopamine was 10 mg. When, however, 10 mg. of dopamine was added to the bath at the height of the contraction caused by 16 μg. of noradrenaline, the aortic strip was partly relaxed.

These observations fit the ideas expressed by Ariëns (1954) that two substances may have similar "affinities" for receptors, but that their "intrinsic activities" when combined with the receptors may differ. Blocking agents are those which have an affinity for the receptors but which have no intrinsic activity. But another substance, which has some intrinsic activity when present alone, may nevertheless reduce the action of a substance having a higher intrinsic activity when it is present together with it. Stephenson (1956) has given a simple example of this in describing the action of butyltrimethylammonium and octyltrimethylammonium on the guinea-pig ileum. The former produced a large contraction in a given dose; the latter produced a small contraction in a much greater dose. However, when both substances were tested together in these same doses, the contraction was not much greater than that caused by the weaker substance acting alone. Stephenson called the weaker stimulant substance a "partial agonist." In his terms dopamine would be a partial agonist, that is a substance which though capable of combining with certain receptor

sites has only a feeble action when it does so. When such a partial agonist is in the presence of a more potent stimulant substance such as noradrenaline which combines with the same receptors, the partial agonist dopamine reduces the effect of the noradrenaline. This reduction can then appear as a fall of blood pressure; hence a fall is produced by a substance which in the absence of noradrenaline causes a rise of blood pressure. Thus the conception of the "partial agonist" provides an explanation for one form of vasomotor reversal.

The foregoing considerations seem to apply not only to the relation between noradrenaline and dopamine but also to the relation between noradrenaline and adrenaline. The relative pressor potency of these substances has been variously given; in the spinal cat Barger and Dale (1910) compared (±)-noradrenaline with (±)-adrenaline, and in different experiments found the ratio to be 1.5 : 1 and 1.25 : 1. During the present experiments we compared the pressor actions in the reserpine-treated cat, and found ratios of 8 : 1 and 4 : 1. Treatment with reserpine removes catechol amines, chiefly noradrenaline, from the artery wall, and the sensitivity of the wall to injected noradrenaline and adrenaline is then greater, particularly to noradrenaline.

In the cat under ether with the vagi cut, a slow infusion of a small amount of adrenaline, such as 5 μg., was found to cause a fall of blood pressure, and also a dilatation of the denervated hindleg (Dale and Richards, 1918). A similar slow infusion of noradrenaline caused a rise of blood pressure and constriction of the denervated hindleg (Burn and Hutcheon, 1949). If, however, the cat was treated with reserpine beforehand, then under the same conditions a slow infusion of 5 μg. of adrenaline caused a rise of blood pressure and constriction of the denervated hindleg. Again this effect was reversed by infusion of noradrenaline, adrenaline causing a fall of blood pressure and vasodilatation of the hindleg. It would therefore appear that the depressor action of small amounts of adrenaline, which was first observed by Moore and Purinton (1900) and which has been the subject of so much investigation, is to be explained in the same way as the depressor action of dopamine. The fall of blood pressure is due to the fact that when adrenaline is attached to receptor sites its efficacy as a constrictor is less than that of noradrenaline. Hence when the receptor sites are occupied by noradrenaline, the injection of adrenaline displaces noradrenaline from some receptors and a fall of blood pressure occurs as a result. However, as Fig. 9 shows, dopamine, being a much weaker constrictor agent than adrenaline, is much more effective in causing a fall.

Our evidence appears to explain one form of vasomotor reversal and so gives rise to the question whether the reversal of the action of adrenaline by ergotamine or by phenoxybenzamine can be similarly explained. We cannot make more than a passing comment on this. Ergotamine is a powerful vasoconstrictor substance (which retains its pressor action in the reserpine-treated spinal cat) and it is therefore possible that the ergotoxine-reversal of adrenaline described by Dale (1906) is similar to the noradrenaline reversal of dopamine. Phenoxybenzamine, however, is not a powerful constrictor substance itself, and it is not possible to suggest that in its presence adrenaline diminishes vascular tone because it is a weaker constrictor substance.

We have found that isoprenaline causes a fall of blood pressure in the reserpine-treated cat when dopamine causes a rise. Thus the effect of isoprenaline must be a direct effect, and implies that there are vasodilator receptors as Dale (1906) originally supposed. His hypothesis that ergotamine blocked the vasoconstrictor receptors, leaving the vasodilator receptors free, would therefore still apply to a substance like dibenzyline and be consistent with all the observations.

This work was done during the tenure by one of us (M. J. R.) of a Fellowship from the Life Insurance Medical Research Fund of Australia and New Zealand. We wish to thank Miss Roneen Hobbs for making the observations on the aorta strips.

ADDENDUM

Sir Henry Dale pointed out to us that in the rabbit adrenaline is a pressor substance under all circumstances. We therefore tested the effect of adrenaline in the rabbit under ether before and during an infusion of noradrenaline. We found that it was pressor before the infusion, but had no effect in any dose during the infusion. We next compared the pressor action of adrenaline with that of noradrenaline in rabbits previously treated with reserpine. We found that adrenaline was equal in pressor action to noradrenaline, whereas in the reserpine-treated cat adrenaline had only one-sixth the pressor action. The relation in the rabbit seems to us to explain why adrenaline is not depressor in that animal.

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