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THE MECHANISM OF THE DEPRESSOR ACTION OF NORADRENALINE IN THE CAT

BY

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In cats anaesthetized with pentobarbitone sodium or chloralose and injected with phenoxybenzamine or phentolamine, administration of (−)-noradrenaline (5 to 20 μg) produced a fall of blood pressure which resembled in onset and duration that produced by adrenaline under similar conditions. The depressor action of noradrenaline was due mainly to dilatation of the splanchnic blood vessels. This could be abolished by administration of pronethalol, a drug known to block sympathetic β-receptors.

According to Euler (1946a, b), Gaddum & Goodwin (1947), Ahlquist (1948), Marsh, Pelletier & Ross (1948) and Nickerson (1949) an intravenous injection of a sympatholytic drug into an anaesthetized cat or dog reverses the pressor response of adrenaline but not that of noradrenaline. West (1949), however, has shown that after treatment with dibenamine or ergotoxine doses of noradrenaline (20 μg or more) produced a fall of blood pressure in cats. This was confirmed by Hazard, Hazard & Mouille (1957) and by Harvey & Nickerson (1953) in anaesthetized rabbits. Furthermore, Melville (1951) has shown that the normal pressor response to intravenous infusion of adrenaline or of noradrenaline can be reversed by an injection of a sympatholytic drug. As a reversal of the pressor effect of noradrenaline has been observed in eighteen out of twenty-three cats treated with phenoxybenzamine (10 to 15 mg/kg) it was thought of interest to investigate the mechanism of this effect.

METHODS

Thirty-three cats (body weight 2.2 to 5.1 kg) were anaesthetized either with sodium pentobarbitone (40 to 45 mg/kg) injected intraperitoneally or with ether followed by an intravenous injection of chloralose (75 mg/kg). The blood pressure was recorded from either a carotid or a femoral artery, heparin (500 U/kg) being used as an anticoagulant. Drugs were usually injected into a femoral vein. In seven of nine cats which were eviscerated, the adrenal glands and the kidneys were left intact, and in the two remainder the adrenal glands were removed.

Contractions of the small intestine were recorded by means of a balloon inserted into its lumen and connected to a float recorder. To assess the rate of blood flow through a hind-limb the blood from the femoral vein was made to pass through a photo-transistor drop-chamber connected to a Gaddum recorder from which it was returned into the proximal end of the same vein. When intra-arterial injections were needed, drugs were injected into a branch of the femoral artery.

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The blood flow in the splanchnic vessels was measured in a similar way. After a ligature had been tied around the pyloric region and around the colon distal to the inferior mesenteric artery, cannulae were fixed into the portal vein, and the portal outflow was diverted to a photo-transistor drop-chamber and returned to the animal through the proximal portal venous cannula. Intra-arterial injections were made through a polyethylene tube into a branch of the superior mesenteric artery supplying the proximal ileum.

Drugs. These were (−)-noradrenaline bitartrate (L. Light and Co.; and Levophed, Bayer Products), (−)-adrenaline acid tartrate B.P. (Burroughs Wellcome), phenoxybenzamine (Dibenyline, Smith, Kline & French Laboratories), phentolamine (Rogitine, Ciba Laboratories Ltd.) and pronethalol (Alderlin, I.C.I.). Phenoxybenzamine was used as a 10 mg/ml. solution in 5% ascorbic acid.

RESULTS

In eight anaesthetized cats treated with either phenoxybenzamine or phentolamine, the effect of intravenous doses of noradrenaline (from 2.5 to 20 μg) on blood pressure was compared with that produced by adrenaline (0.5 to 4 μg). Both drugs produced a fall of blood pressure which varied with the amounts injected, though the effect of adrenaline was always greater than that of noradrenaline. This is shown in Table 1. In all these experiments the sympathomimetic drugs were injected at

TABLE 1

COMPARISON OF THE DEPRESSOR ACTIVITY OF (−)-ADRENALINE AND (−)-NORADRENALINE GIVEN AT TWO DOSE LEVELS IN CATS TREATED WITH PHENOXYBENZAMINE OR PHENTOLAMINE

The dose of phenoxybenzamine was 15 mg/kg, and that of phentolamine was 2 mg/kg. Dose-ratio gives the ratio of doses of adrenaline to noradrenaline needed to give equal falls of blood pressure

Expt. no.	Anaesthetic	Blocking drug	Doses (μg) of Adrenaline	Doses (μg) of Noradrenaline	Dose-ratio
1	Pentobarbitone	Phenoxybenzamine	0·5 1·0	2·5 5·0	5·2
2	Pentobarbitone	Phenoxybenzamine	1·0 2·0	10·0 20·0	11·1
3	Pentobarbitone	Phentolamine	0·5 1·0	5·0 10·0	12·0
4	Pentobarbitone	Phentolamine	1·0 2·0	6·0 12·0	8·7
5	Chloralose	Phenoxybenzamine	2·0 4·0	8·0 16·0	7·8
6	Chloralose	Phenoxybenzamine	1·0 2·0	8·0 16·0	7·3
7	Chloralose	Phentolamine	2·0 4·0	10·0 20·0	8·9
8	Chloralose	Phentolamine	1·0 2·0	5·0 10·0	6·3

5 min intervals, the first injection being given 15 min after administration of phentolamine or phenoxybenzamine. The magnitude of the depressor effects produced either by noradrenaline or by adrenaline were not affected either by administration

of atropine (2.5 mg/kg) or by exclusion of the adrenal glands and the liver from the circulation. They could, however, be prevented by intravenous administration of pronethalol (5 mg/kg) (Fig. 1).

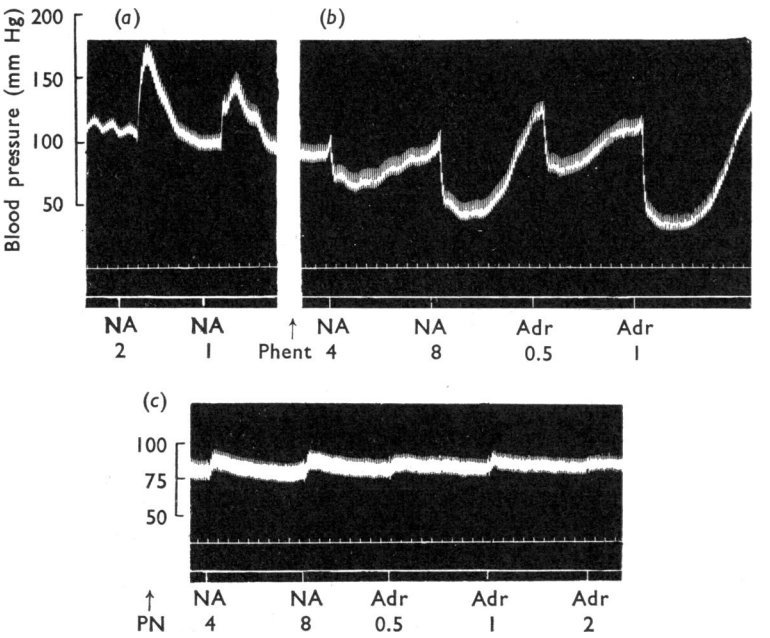

Fig. 1. Effect of phentolamine (Phent, 2 mg/kg) and of pronethalol (PN, 5 mg/kg) on the response of the blood pressure of a cat (1.8 kg) to intravenous injections of adrenaline (Adr) and noradrenaline (NA); doses in μg. (*b*) was taken 15 min after administration of phentolamine and (*c*) was 15 min after intravenous administration of pronethalol. Time marks: 30 sec.

According to Black & Stephenson (1962) and Vanov (1963) pronethalol blocks the sympathetic β-receptors responsible for the depressor activity of adrenaline and isoprenaline. This was confirmed in experiments in which administration of pronethalol antagonized the fall of blood pressure produced either by adrenaline, isoprenaline or noradrenaline without interfering with that produced by histamine, acetylcholine, methacholine, carbachol or with that due to the stimulation of the peripheral end of the vagus in the cat (Fig. 2).

As pronethalol appeared to antagonize the depressor effect of noradrenaline it was decided to examine the effects of noradrenaline during adrenergic blockade on the vessels of the skeletal muscle and on the splanchnic vessels.

Effect on vessels of skeletal muscle. To isolate the effects of noradrenaline on the vessels of the limb from those which would result from changes of the systemic blood pressure, a carotid artery was connected to a blood pressure stabilizer as described by Ginzel & Kottegoda (1954). Whether injected intravenously (1 to 20 μg) or intra-arterially (0.1 to 2 μg) noradrenaline always caused vasoconstriction, as assessed from changes in blood flow (six experiments). This effect could be

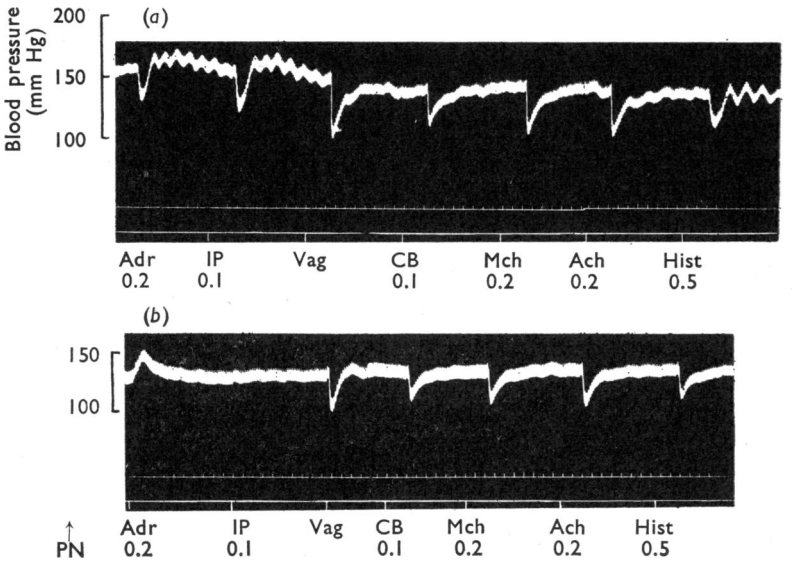

Fig. 2. Effect of pronethalol (PN, 5 mg/kg) on the blood pressure response of a cat (3.1 kg) to intravenous injections of adrenaline (Adr), isoprenaline (IP), carbachol (CB), methacholine (Mch), acetylcholine (Ach), histamine (Hist) and to stimulation of the peripheral end of a vagus nerve (Vag, 2 V, 20 shocks/sec, 1 msec); doses in μg. (*b*) was taken 15 min after the administration of pronethalol. Time marks: 30 sec.

abolished by administration of either phenoxybenzamine (10 mg/kg) or phentolamine (2 mg/kg). In two experiments large doses of noradrenaline (1 μg close-arterial and 5 to 10 μg intravenous injections) produced an increase of blood flow through the limb; this, however, could be abolished by increasing the dose of the sympatholytic drug (20 mg/kg of phenoxybenzamine) (Fig. 3).

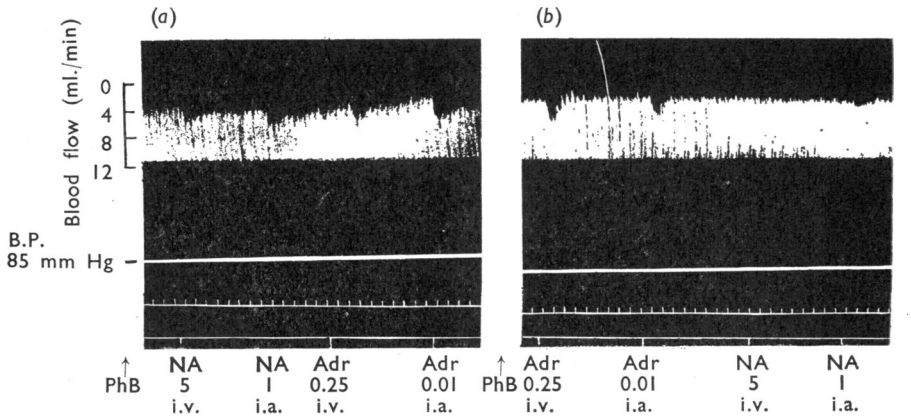

Fig. 3. Effect of phenoxybenzamine (PhB) on the responses of hind-limb blood flow of a cat (3.4 kg) to adrenaline (Adr) and noradrenaline (NA); doses in μg. I.v., intravenous; i.a., close-arterial injection. Phenoxybenzamine (10 mg/kg) was given intravenously before (*a*); (*b*) was taken 15 min after the administration of a second dose of phenoxybenzamine (20 mg/kg). Blood pressure was stabilized throughout the experiment. Time marks: 30 sec.

In contrast in all these experiments, adrenaline (0.01 μg close-arterial and 0.25 μg intravenous injections) caused an increase in the blood flow which was not affected either by atropine (2.5 mg/kg) or even by a large dose of phenoxybenzamine (30 mg/kg); it was abolished, however, by pronethalol (5 mg/kg).

Effect on splanchnic vessels. The effect of noradrenaline on the blood flow in the splanchnic vascular bed was recorded in seven experiments in which the blood pressure was stabilized. In the absence of a sympatholytic drug, noradrenaline (0.1 μg intra-arterial or 1 μg intravenous injections) produced a decrease in blood flow. As the systemic blood pressure was kept constant, this indicated a vasoconstriction. After administration of phenoxybenzamine (10 to 15 mg/kg) or phentolamine (2 mg/kg) the constrictor effect of noradrenaline was abolished. Increasing the doses of noradrenaline to 0.5 μg by close-arterial or 5 μg by intravenous injection produced an increase in blood flow, thus unmasking a dilator response. At this stage adrenaline (injections of 0.25 μg intra-arterially or 1.0 μg intravenously) also increased the blood flow. The vasodilation produced both by adrenaline and by noradrenaline was unaffected by subsequent administration of atropine (2.5 mg/kg) or by increasing the dose of the sympatholytic drug (phenoxybenzamine, 30 mg/kg) but was completely abolished by an intravenous injection of pronethalol (5 mg/kg) (Fig. 4).

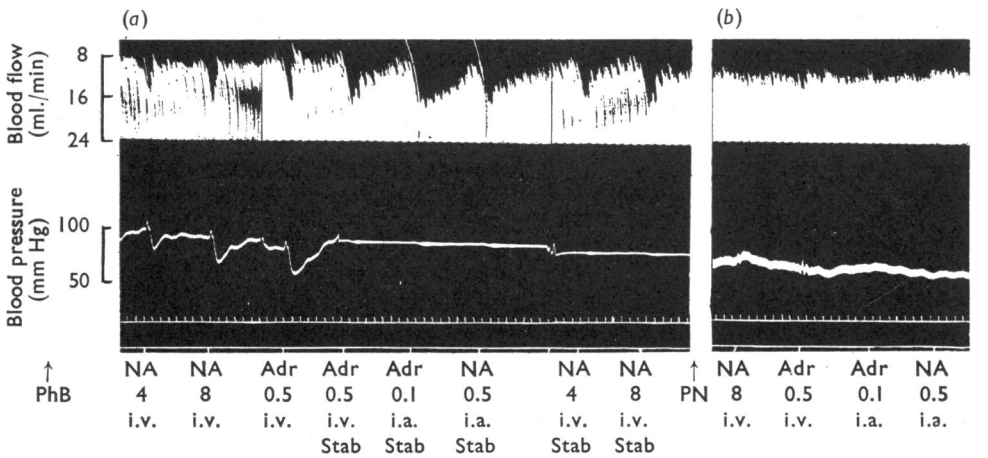

Fig. 4. Effect of pronethalol (PN), 5 mg/kg, on responses to noradrenaline (NA) and adrenaline (Adr) in a cat (3.1 kg) treated with phenoxybenzamine (PhB, 15 mg/kg). Lower tracing, blood pressure; upper tracing, splanchnic blood flow. (*b*) was taken 20 min after the administration of pronethalol. Phenoxybenzamine was administered 30 min before the beginning of the experiment. Time marks: 30 sec. I.v., intravenous; i.a., close-arterial injection. Stab, blood pressure stabilized.

Effect of evisceration. In six out of seven eviscerated cats treated with either phenoxybenzamine (15 mg/kg) or phentolamine (2 mg/kg), injections of noradrenaline (1 to 20 μg) no longer produced any vasodepression. In the eviscerated cats the depressor effect of adrenaline was reduced but not completely suppressed (Fig. 5) irrespective of whether the liver, the adrenal glands and the kidneys had been removed as well as the stomach and intestine.

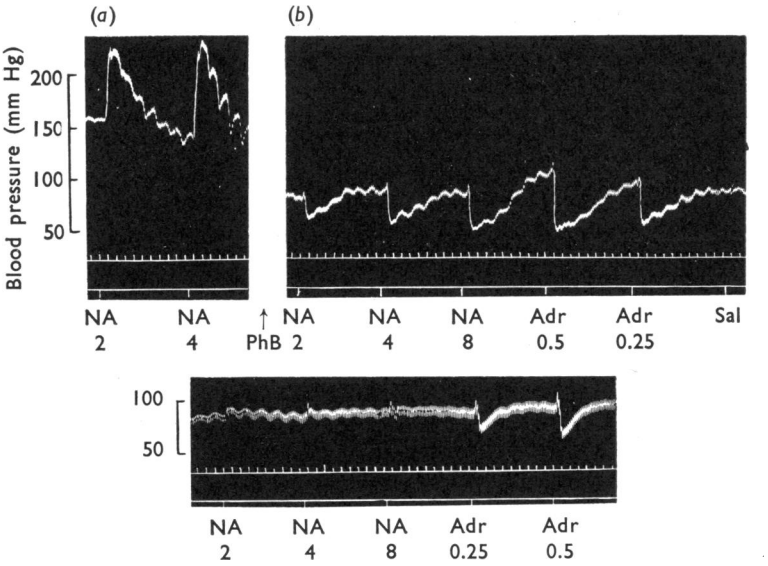

Fig. 5. Effect of evisceration on the responses of blood pressure of a cat (3.3 kg) to intravenous injection of adrenaline (Adr) and noradrenaline (NA). Doses in μg. Sal, 1 ml. of 0.9% isotonic saline. (*b*) was taken 15 min after intravenous administration of phenoxybenzamine (PhB, 15 mg/kg), and (*c*) 15 min after evisceration of the animal. Time marks: 30 sec.

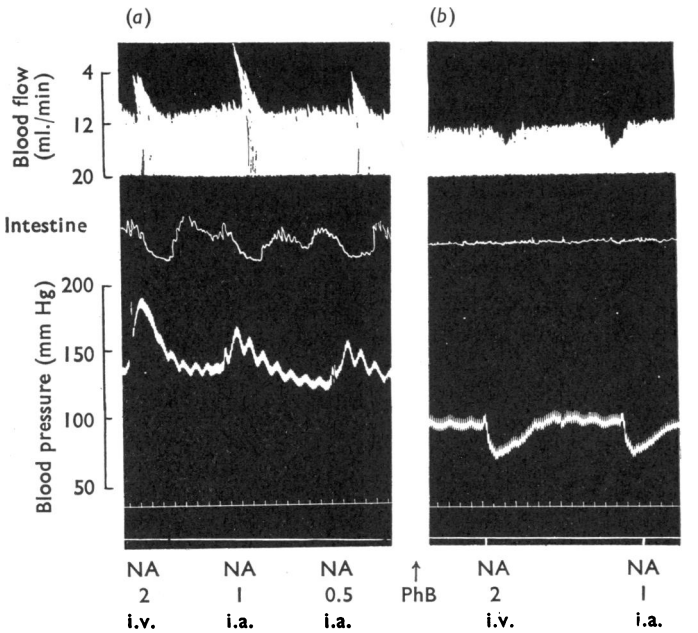

Fig. 6. Effect of phenoxybenzamine (PhB, 20 mg/kg) on the responses of splanchnic blood flow, the movements of the small intestine, and the blood pressure of a cat (2.6 kg) injected intravenously with adrenaline (Adr) and noradrenaline (NA); doses in μg. I.v., intravenous; i.a., close-arterial injection. (*b*) was taken 20 min after the administration of phenoxybenzamine. Time marks: 30 sec.

Effect of noradrenaline on the contraction of the intestine. In two experiments noradrenaline inhibited the contractions of the small intestine, when injected intravenously (1 to 4 μg) or close-arterially (0.5 to 2 μg); phenoxybenzamine (20 mg/kg) antagonized this effect in one experiment and in the other it reduced it by approximately 80% (Fig. 6).

DISCUSSION

The transformation of the vasopressor effect of adrenaline into a depressor effect by sympatholytic drugs is due to the suppression of the vasoconstrictor action. From the present investigation it appears that the fall of blood pressure produced by noradrenaline during adrenergic blockade may also be due to a similar mechanism. According to Burn & Hutcheon (1949) both noradrenaline and adrenaline dilate the coronary vessels of the anaesthetized cat and dog and both also dilate the vessels of the rabbit's ear in the presence of a sympatholytic agent. Furthermore, according to the same authors small doses of noradrenaline, even in the absence of a sympatholytic drug, dilate intestinal loops of the anaesthetized cat. Whether this effect is due to dilatation of the intestinal blood vessels or to a specific action of the drug on the smooth muscle of the intestine is not clear.

In the present experiments it could be shown that noradrenaline dilates the blood vessels of the splanchnic region during blockade of α-receptors. As noradrenaline did not produce a fall of blood pressure in eviscerated cats it is conceivable that the blood vessels of this region may be responsible for the depressor effect of this drug. This is indirectly supported by the observation that in non-eviscerated cats the dilatation of splanchnic blood vessels and the resultant fall in blood pressure can both be antagonized by pronethalol.

It is known that large doses of noradrenaline can produce a reflex dilatation of the blood vessels in the femoral vascular bed in the absence of a sympatholytic drug (Gruhzit, Freyborger & Moe, 1954). It is unlikely, however, that this can be the cause of the fall of the systemic blood pressure produced by noradrenaline since the reflex vasodilatation can be abolished by sympatholytic drugs (Oswald, 1960). The small increase in blood flow observed in the hind-limbs in two cats out of six could be of reflex origin since it was abolished by increasing the dose of the sympatholytic drug.

Folkow, Frost & Uvnäs (1948) have suggested that the fall in blood pressure produced by stimulation of the sympathetic supply to the splanchnic vessels may be due to a decrease of the peripheral vascular resistance occurring as a result of the relaxation of the gastro-intestinal tract. In two experiments, however, phenoxybenzamine (20 mg/kg) abolished almost completely the relaxation of the smooth muscle of the intestine, though the blood flow still increased (Fig. 6). West (1949) has suggested that the fall in blood pressure following the administration of noradrenaline may be due to constriction of the branches of the portal vein in the liver. In two experiments, however, in which the blood from the portal vein before it entered the liver had been diverted into a femoral vein and the hepatic artery had been tied, a fall of blood pressure still resulted. As the increase of blood flow and the depressor effects produced both by adrenaline and by noradrenaline are

not affected by either atropine or phenoxybenzamine, but are selectively antagonized by pronethalol, it would appear that the vasodilator action of noradrenaline must be exerted on sympathetic β-receptors.

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