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THE MECHANISM OF THE PRESSOR ACTION OF NORADRENALINE IN PITHED CATS

BY

S. M. M. KARIM*

From the Department of Physiology and Pharmacology, Chelsea College of Science and Technology, London, S.W.3

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Although noradrenaline acts directly on the isolated mammalian heart to increase its rate and force of contraction, in the intact animal this action is masked by reflex compensatory bradycardia, and hence the rise in arterial blood pressure produced by noradrenaline is the result only of peripheral vasoconstriction (Barcroft & Konzett, 1949; Barnett, Blacket, Depoorter, Sanderson & Wilson, 1950; Goldenberg, Aranow, Smith & Faber, 1950; Bearn, Billing, Sherlock & Sherlock, 1951; King, Sokoloff & Wechsler, 1952). Various drugs have been shown to abolish the pressor action of noradrenaline in anaesthetized animals by antagonizing its vasoconstrictor action. This has been demonstrated for ergot alkaloids, yohimbine, tolazoline, phentolamine, phenoxybenzamine and dibenamine (West, 1949; Dekanski, 1951; Innes & Kosterlitz, 1951; Gross & Stricker, 1950; Barnett & Fowler, 1952; Polonovski, Schmitt & Pelou, 1952; Withrington & Zaimis, 1961; Butterworth, 1963).

However, it has been repeatedly observed in this laboratory that phenoxybenzamine and phentolamine, in doses which abolish the pressor action of noradrenaline in normal anaesthetized cats and rats, fail to abolish the pressor action of noradrenaline in preparations that have been pithed. The present study was undertaken in an attempt to determine the mode of action of noradrenaline in increasing the arterial blood pressure in pithed cats.

METHODS

Cats weighing 2.4 to 3.1 kg were anaesthetized either with pentobarbitone sodium (40–45 mg/kg) injected intraperitoneally or with ether followed by an intravenous injection of chloralose (80 mg/kg). The blood pressure was recorded from a cannulated femoral artery by means of a mercury manometer. Heparin (500 u.) was used as an anticoagulant in the arterial cannula. Drugs were injected intravenously via a cannula tied into the left femoral vein and washed into the circulation with 1 ml. of 0.9 w/v sodium chloride solution. Heart rates were recorded by the method of Daly & Schweitzer (1950).

Spinal cats were prepared by a procedure as described by Burn (1952).

Pithed cats. The spinal cord was destroyed by the passage of a rod down the length of the vertebral canal. Both spinal and pithed cats were rested for one hour before they were used for experiments.

* Present address: Institute of Obstetrics and Gynaecology, University of London, Queen Charlotte's Hospital, Goldhawk Road, London, W.6.

The methods for measuring the blood flow in the splanchnic and femoral vascular beds have been previously described (Karim, 1964).

Acute cardiac sympathetic denervation was carried out in chloralosed cats with an open chest under positive artificial respiration either by the removal of the sympathetic chain from the stellate ganglia to the level of T 5, or by cutting the postganglionic cardiac sympathetic nerves.

In some experiments the postganglionic cardiac sympathetic nerves on the right side were continuously stimulated with rectangular pulses of 0.5 msec duration at a frequency of 5–10 shocks/sec and at a strength of between 4 and 8 v.

Cardiac output was measured by the direct Fick method. The method has been previously described (Karim, 1965).

Drugs

Adrenaline acid tartrate B.P. (Burroughs Wellcome); (−)-noradrenaline bitartrate (Bayer); methoxamine hydrochloride, B.P.C. (Burroughs Wellcome) and phenylephrine hydrochloride, B.P.C. (Koch-Light) were used. Doses of these drugs are given in terms of the base.

Phentolamine (Ciba); pronethalol (I.C.I.) and vasopressin (Parke Davies) were also used. Phenoxybenzamine (Smith, Kline & French) was dissolved in 5% ascorbic acid solution.

RESULTS

Anaesthetized Cats

(*a*) *Blood Pressure.* The effect of phenoxybenzamine (10 mg/kg) or phentolamine (2 mg/kg) on the changes in arterial blood pressure and heart rate produced by noradrenaline was investigated in eight cats anaesthetized with pentobarbitone sodium or chloralose. A graded pressor response to noradrenaline was obtained by injecting three doses of the drug (0.125, 0.25, and 0.5 μg/kg) at intervals of 5 min. Phenoxybenzamine (10 mg/kg) or phentolamine (2 mg/kg) was then injected intravenously. Thirty min later the doses of noradrenaline were repeated. Under these conditions the pressor action of the three doses of noradrenaline was abolished in all these experiments. (Fig. 1, Table I).

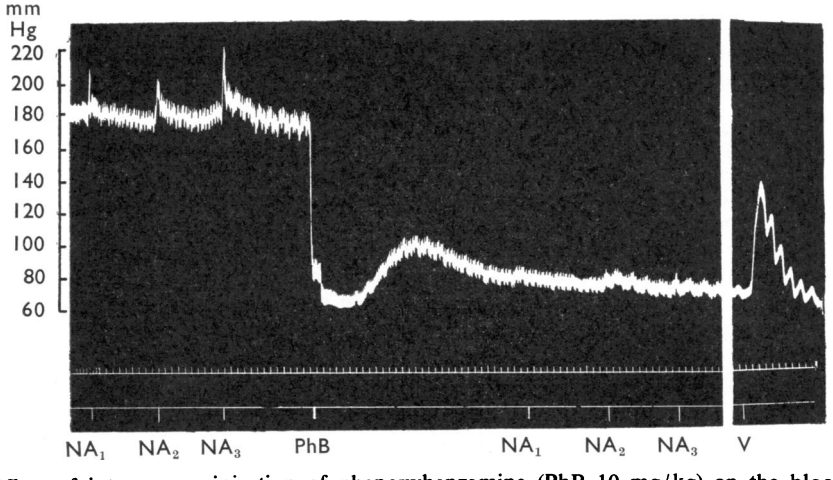

Fig. 1. Effect of intravenous injection of phenoxybenzamine (PhB 10 mg/kg) on the blood pressure of a chloralose cat (2.1 kg) to intravenous injections of noradrenaline (NA_1, NA_2, NA_3, 0.125, 0.25 and 0.5 μg/kg resp.) and of vasopressin (V, 0.2 mU). Time marks: 30 sec.

TABLE 1

EFFECT OF PHENOXYBENZAMINE AND PHENTOLAMINE ON THE BLOOD PRESSURE AND HEART RATE RESPONSES OF CHLORALOSED CATS TO NORADRENALINE

B.P.= Arterial blood pressure mm Hg. H.R.= Heart rate per min. (+) = Increase in blood pressure or heart rate; (−) = decrease in blood pressure or heart rate. 0 indicates no change. The range of values representing the mean are shown in parentheses

Treatment (No. of cats)	Before noradrenaline		Changes after noradrenaline (i.v.)					
			0·125 μg/kg		0·25 μg/kg		0·5 μg/kg	
	B.P.	H.R.	B.P.	H.R.	B.P.	H.R.	B.P.	H.R.
Control (2)	120 (110 to 130)	190 (170 to 210)	+22 (19 to 25)	−12 (−10 to −14)	+34 (30 to 38)	−8 (−2 to −14)	+48 (44 to 52)	−18 (−8 to −28)
Phenoxybenzamine (10 mg/kg) (i.v.)	70 (60 to 80)	180 (160 to 200)	0 —	+10 (10)	0 —	+20 (16 to 24)	0 —	+26 (22 to 30)
Control (2)	140 (130 to 150)	186 (180 to 196)	+22 (18 to 26)	+6 (2 to 10)	+38 (30 to 46)	−4 (0 to −8)	+52 (47 to 57)	−12 (−8 to −16)
Phentolamine (2 mg/kg) (i.v.)	90 (80 to 100)	170 (165 to 175)	0 —	+8 (6 to 10)	0 —	+18 (12 to 24)	0 —	+30 (22 to 38)

Heart rate. When noradrenaline was injected before the administration of phenoxybenzamine or phentolamine, it produced tachycardia in two cats but in the remaining six cats the pressor action of noradrenaline was accompanied by a slowing of the heart. After injection of one or other of the antagonists, the three concentrations of noradrenaline produced tachycardia in all eight experiments.

Spinal cats. In four spinal cats intravenous injections of noradrenaline (0.125, 0.25 and 0.5 μg/kg) produced graded increases in blood pressure and heart rate. The pressor responses, however, did not differ significantly from those obtained with the same doses of noradrenaline in anaesthetized cats. Intravenous injections of phenoxybenzamine (10 mg/kg) or phentolamine (2 mg/kg) abolished the pressor effects of the three doses of noradrenaline without modifying its positive chronotropic effect (Table 2).

TABLE 2

EFFECT OF PHENOXYBENZAMINE AND PHENTOLAMINE ON THE BLOOD PRESSURE AND HEART RATE RESPONSES OF SPINAL CATS TO NORADRENALINE

B.P.= Arterial blood pressure, mm Hg; H.R.= heart rate per min. 0 indicates no change. The range of values representing the mean are shown in parentheses

No. of experiments and treatment	Before noradrenaline		Increases after noradrenaline (i.v.)					
			0·125 μg/kg		0·25 μg/kg		0·5 μg/kg	
	B.P.	H.R.	B.P.	H.R.	B.P.	H.R.	B.P.	H.R.
Control (4)	85 (70 to 100)	162 (140 to 180)	26 (18 to 32)	11 (7 to 16)	40 (28 to 48)	16 (10 to 19)	54 (40 to 64)	24 (14 to 29)
Phenoxybenzamine, 10 mg/kg (2) (i.v.), or Phentolamine, 2 mg/kg (2) (i.v.)	60 (50 to 80)	165 (150 to 175)	0 —	12 (8 to 18)	0 —	16 (12 to 22)	0 —	25 (19 to 30)

Pithed cats. Noradrenaline in doses of 0.125, 0.25 and 0.5 μg/kg gave pressor responses of 50, 65.5 and 93.5 mm Hg (mean values). These responses were significantly greater than those produced by the same doses of noradrenaline in either anaesthetized or spinal cats. When the same doses of noradrenaline were given after treatment with the antagonists, the pressor effects were correspondingly reduced to 31.5, 39.5 and 50.0 mm Hg (mean vaues); a reduction of less than 50%. Increasing the concentration of phenoxybenzamine (20 mg/kg) or phentolamine (5 mg/kg) did not reduce the pressor action of noradrenaline any further (Fig. 2, Table 3).

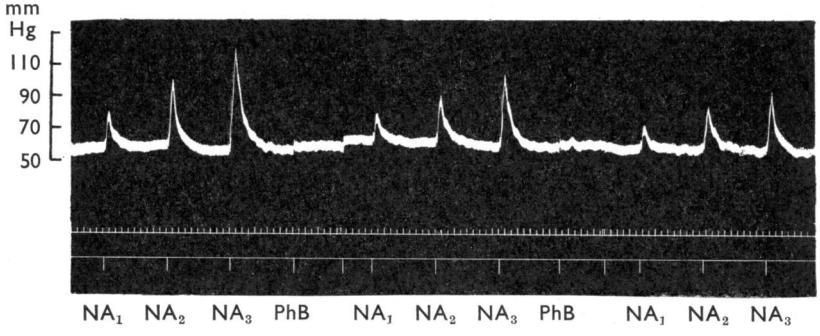

Fig. 2. Effect of intravenous injections of phenoxybenzamine (PhB 10 mg/kg) on the response of the blood pressure of a pithed cat (2.5 kg) to intravenous injections of noradrenaline (NA_1, NA_2, NA_3 0.125, 0.25 and 0.5 μg/kg resp.) Time marks: 30 sec.

TABLE 3

EFFECT OF PHENOXYBENZAMINE AND PHENTOLAMINE ON THE BLOOD PRESSURE AND HEART RATE RESPONSES OF PITHED CATS TO NORADRENALINE

B.P.= Arterial blood pressure, mm Hg; H.R.= heart rate per min. 0 indicates no change. The range of values representing the mean are shown in parentheses

No. of experiments and treatment	Before noradrenaline		Increases after noradrenaline (i.v.) 0·125 μg/kg		0·25 μg/kg		0·5 μg/kg	
	B.P.	H.R.	B.P.	H.R.	B.P.	H.R.	B.P.	H.R.
Control (4)	60 (50 to 70)	115 (100 to 130)	50 (45 to 60)	11 (7 to 15)	66 (56 to 78)	23 (14 to 31)	93 (82 to 105)	33 (27 to 40)
Phenoxybenzamine, 10 mg/kg (2) (i.v.), or Phentolamine, 2 mg/kg (2) (i.v.)	60 (60)	122 (100 to 130)	30 (25 to 35)	11 (8 to 16)	39 (32 to 46)	23 (18 to 29)	50 (44 to 60)	33 (28 to 40)

In two chloralosed cats it was shown that when the pressor response to noradrenaline (0.25 and 0.5 μg/kg) was previously abolished with phenoxybenzamine (10 mg/kg), pithing the cats caused a reappearance of at least 50% of the pressor action of noradrenaline. (Fig. 3.)

Since noradrenaline is known to increase the blood pressure by peripheral vasoconstriction, blood flow studies in the femoral and splanchnic vascular beds were carried out

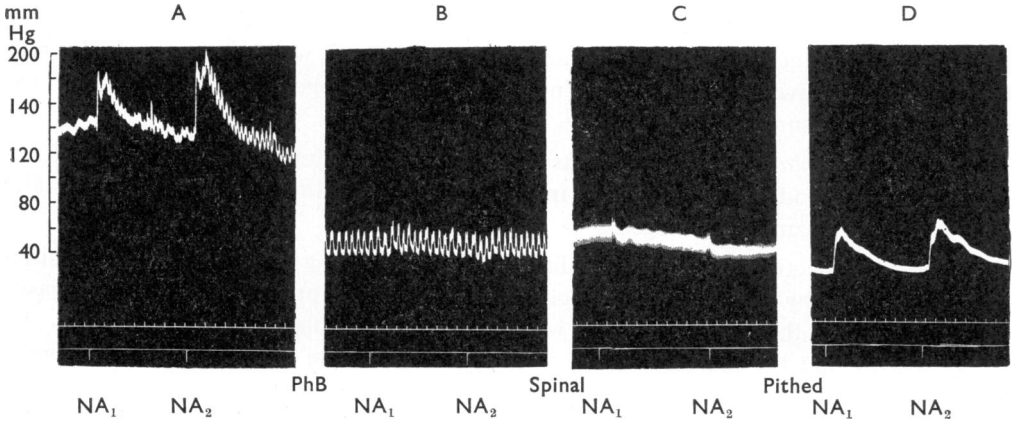

Fig. 3. Effect of intravenous injection of phenoxybenzamine (PhB 10 mg/kg) on the response of the blood pressure of a chloralose cat (2.2 kg) to noradrenaline (NA_1, NA_2, 0.25 and 0.5 μg/kg resp.) (B) Was taken 30 min after the administration of phenoxybenzamine ; (C) was taken 30 min after cutting the spinal cord between C_1 and C_2 ; and (D) was taken 60 min after pithing the entire cord. Time marks: 30 sec.

in an attempt to discover the mechanism of the pressor action of noradrenaline in the pithed cat.

Blood flow studies. The effect of noradrenaline on the arterial blood pressure and the blood flow through one hind limb was recorded in two experiments under chloralose anaesthesia and in two pithed cats. In a similar manner the effect of noradrenaline on the arterial blood pressure and the blood flow in the splanchnic vascular bed was recorded in two chloralosed and in two pithed cats. The procedure following in all these experiments was as follows. Responses to two different doses of noradrenaline injected intravenously, and to two doses injected close-arterially into the vascular bed under investigation, were recorded on the arterial blood pressure and the blood flow. When the effect of intravenously injected noradrenaline on the blood flow was studied, the same doses were injected both before and after connecting a blood pressure stabilizer to the carotid artery. It was possible by this procedure to isolate the direct effect of noradrenaline on the vessels of the area under investigation from the indirect effect due to the change in the systemic blood pressure.

Anaesthetized cats

(*a*) *Femoral vascular bed.* In the two experiments on chloralosed cats, intra-arterial injections of noradrenaline (0.025 and 0.05 μg/kg) produced a decrease in blood flow through the hind limb but no change in arterial blood pressure, indicating vasoconstriction.

Intravenous injections of noradrenaline (0.25 and 0.5 μg/kg) raised the blood pressure, and there was an initial increase followed by a more marked decrease in flow. When the carotid artery was connected to the blood pressure stabilizer, the initial increase in flow was absent and the reduction in flow became much greater.

Thirty min after the injection of phenoxybenzamine (10 mg/kg i.v.) the decrease in blood flow produced by noradrenaline (intra-arterially as well as intravenously) was abolished and intravenous injection of noradrenaline no longer produced a rise of the arterial blood pressure (Table 4).

Splanchnic vascular bed. In two cats intra-arterial injections of noradrenaline (0.05 and 0.1 μg/kg) produced a reduction in blood flow indicating vasoconstriction. The blood pressure remained unchanged.

Intravenous injections of noradrenaline (0.25 and 0.5 μg/kg) produced an initial increase followed by a decrease in blood flow. This was converted into a pure vasoconstriction when the blood pressure was stabilized. In both these experiments the vasoconstrictor and the pressor actions of noradrenaline were abolished by intravenous doses of phenoxybenzamine (10 mg/kg).

Pithed cats. The effect of noradrenaline on the arterial blood pressure and blood flow in the splanchnic and femoral beds was similar to those recorded in anaesthetized cats.

When responses to noradrenaline were tested after the injection of phenoxybenzamine (10 mg/kg), the reduction in blood flow previously produced by intravenous and intra-arterial injections of noradrenaline was abolished in the splanchnic and femoral vascular beds. However, phenoxybenzamine failed to abolish the pressor effects of intravenously injected noradrenaline. The maximum reduction of the pressor action of intravenous noradrenaline was approximately 45% (Tables 4 and 5. Fig. 4).

Effect of phenoxybenbzamine on the blood pressure response of pithed cats to other sympathomimetic amines

In the pithed cat previously injected with adrenaline antagonists, the pressor action of noradrenaline is probably due to a mechanism other than vasoconstriction. It was therefore desirable to investigate the effect of phenoxybenzamine on the pressor action

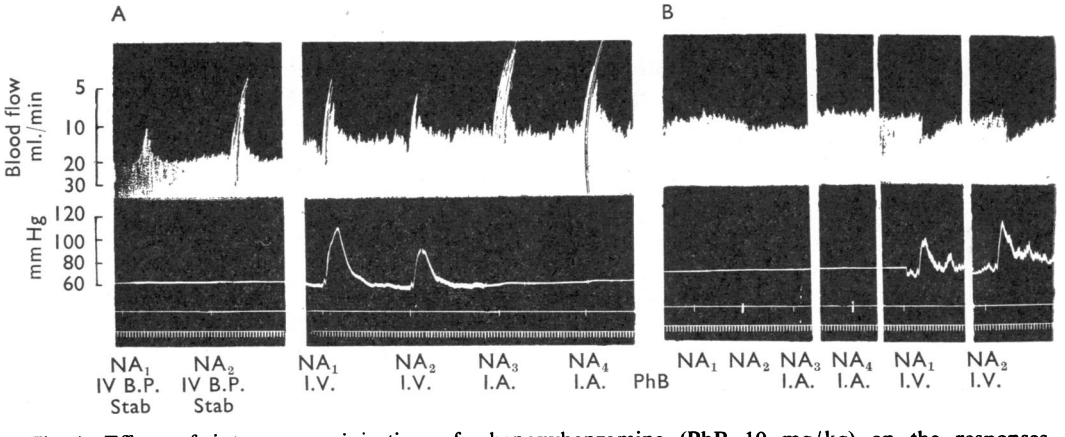

Fig. 4. Effect of intravenous injection of phenoxybenzamine (PhB 10 mg/kg) on the responses of splanchnic blood flow (upper tracing) and arterial blood pressure (lower tracing) of a pithed cat (2.8 kg) to intravenous injections (i.v.) of noradrenaline (NA_1, NA_2, 0.25 and 0.5 μg/kg resp.) and to intra-arterial (i.a.) injections of noradrenaline (NA_3, NA_4, 0.05 and 0.1 μg/kg resp.) (B) was taken 30 min after the administration of phenoxybenzamine. Time marks: 30 sec. B.P. Stab: Blood pressure stabilized.

TABLE 4

EFFECT OF PHENOXYBENZAMINE ON THE BLOOD FLOW RESPONSES OF THE FEMORAL VASCULAR BED OF ANAESTHETIZED AND PITHED CATS TO NORADRENALINE

(+) Increase in blood flow. (−) Decrease in blood flow. Responses to intravenous injections of noradrenaline on the blood flow were recorded after stabilizing the blood pressure. (0) Indicates no change in blood flow. The range of values representing the mean are shown in parentheses

	Before phenoxybenzamine						After phenoxybenzamine				
		Changes in blood flow after injecting noradrenaline						Changes in blood flow after injecting noradrenaline			
		Intravenous		Intra-arterial				Intravenous		Intra-arterial	
Number of experiments and treatment	Control blood flow (ml./min)	0·25 μg/kg	0·5 μg/kg	0·025 μg/kg	0·05 μg/kg	Dose	Control blood flow (ml./min)	0·25 μg/kg	0·5 μg/kg	0·025 μg/kg	0·05 μg/kg
Two cats anaesthetized with chloralose	18·4 (14·5 to 22·3)	−4·2 (−3·0 to −5·4)	−7·1 (−6·2 to −8·0)	−4·8 (−3·2 to −6·4)	−8·2 (−6·7 to −9·7)	Phenoxybenzamine 10 mg/kg (i.v.)	19·8 (15·4 to 23·2)	0	0	0	0
Two pithed cats	12·0 (9·8 to 14·20	−3·9 (−3·4 to −4·4)	−7·8 (−7·0 to −8·6)	−3·8 (−3·2 to −4·4)	−7·9 (−6·8 to −9·0)	Phenoxybenzamine 10 mg/kg (i.v.)	11·5 (9·5 to 13·5)	0	0	0	0

TABLE 5

EFFECT OF PHENOXYBENZAMINE ON THE BLOOD FLOW RESPONSES IN THE SPLANCHNIC VASCULAR BED OF ANAESTHETIZED AND PITHED CATS TO NORADRENALINE

(+) Increase in blood flow. (−) Decrease in blood flow. Responses to intravenous injections of noradrenaline on the blood flow were recorded after stabilizing the blood pressure. (0) Indicates no change in blood flow. Mean values with range in parentheses

	Before phenoxybenzamine						After phenoxybenzamine				
		Changes in blood flow after injecting noradrenaline						Changes in blood flow after injecting noradrenaline			
		Intravenous		Intra-arterial				Intravenous		Intra-arterial	
Number of experiments	Control blood flow (ml./min)	0·25 μg/kg	0·50 μg/kg	0·05 μg/kg	0·1 μg/kg	Dose (mg/kg) (i.v.)	Control blood flow (ml./min)	0·25 μg/kg	0·50 μg/kg	0·05 μg/kg	0·1 μg/kg
Two cats anaesthetized with chloralose	32·8 (26·3 to 39·3	−6·4 (−5·1 to −7·7)	−13·4 (−11·9 to −14·9)	−8·3 (−7·8 to −8·8)	−15·9 (−14·1 to −17·7)	10	30·0 (27·1 to 32·9)	0	0	0	0·8 (0 to 1·6)
Two pithed cats	26·4 (22·8 to 30·0)	−4·8 (−3·9 to −5·7)	−8·1 (−6·8 to −9·4)	−5·7 (−4·8 to −6·6)	−11·5 (−8·9 to −14·1)	10	29·9 (24·3 to 35·5)	0	0	0	(0·4 to 0·8)

of sympathomimetic amines which produce only vasoconstriction and lack cardiac stimulant action. Methoxamine and phenylephrine were used (Hjort, Randall & De Beer, 1948 ; Stutzman, Pettinga & Fruggiero, 1949).

In two pithed cats intravenous injections of methoxamine (25 μg/kg) produced an immediate rise of the arterial blood pressure which lasted for 4–20 min. Whereas the pressor action of noradrenaline was accompanied by an increase in heart rate, that of the other two amines was not. Phenoxybenzamine (10 mg/kg) abolished the pressor actions of methoxamine and phenylephrine but the pressor action of noradrenaline was only reduced by half. (Fig. 5.)

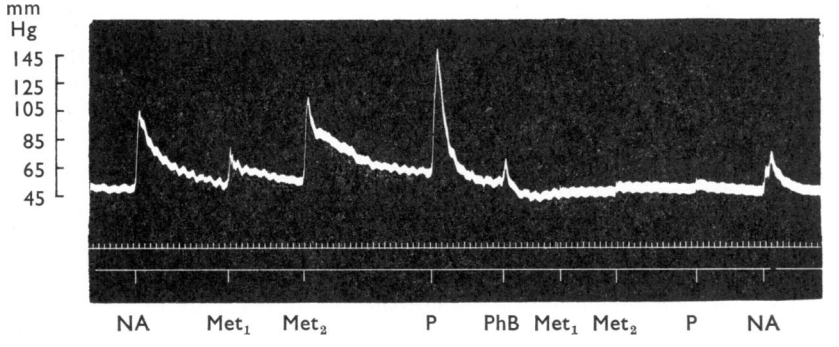

Fig. 5. Effect of intravenous injection of phenoxybenzamine (PhB 10 mg/kg) on the blood pressure response of a pithed cat (2.3 kg) to intravenous injections of noradrenaline (NA, 0.5 μg/kg), methoxamine (Met_1, Met_2, 10 and 25 μg/kg resp.) and phenylephrine (P, 5 μg/kg). Time marks: 30 sec.

The results of these experiments indicate that phenoxybenzamine abolished the vasoconstrictor action of sympathomimetic amines and support the suggestion that the pressor action of noradrenaline in the presence of phenoxybenzamine in the pithed cat is not due to vasoconstriction. The mechanism of the pressor action was investigated in further experiments.

According to Eckstein & Hosley (1961) and Zimmerman, Brody & Beck (1960) removal of the sympathetic tone to the heart causes a reduction in heart rate, cardiac output and ventricular work. It is therefore conceivable that in pithed cats, because of the loss of sympathetic tone, noradrenaline increases arterial blood pressure by an action on the heart. The following experiments were performed to test this view.

The effect of phenoxybenzamine on the arterial blood pressure responses of anaesthetized cats with sympathetically denervated hearts to noradrenaline

In two chloralosed cats with sympathetically denervated hearts, intravenous injections of noradrenaline (0.125, 0.25 and 0.5 μg/kg) produced an average increase in arterial blood pressure of 50, 64 and 90 mm Hg respectively. When the same doses of noradrenaline were repeated after a dose of phenoxybenzamine (10 mg/kg i.v.), the average increase in arterial blood pressure produced by the same three doses of noradrenaline was 28, 36 and 46 mm Hg respectively (Fig. 6).

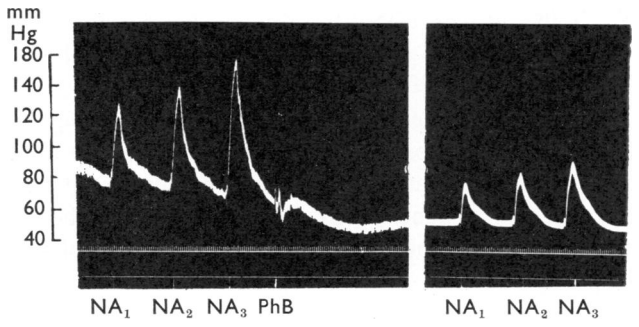

Fig. 6. Effect of intravenous injection of phenoxybenzamine (PhB 10 mg/kg) on the response of the blood pressure of a chloralose cat (3.2 kg) with sympathetically denervated heart to intravenous injections of noradrenaline (NA_1, NA_2, NA_3, 0.125, 0.25 and 0.5 μg/kg resp.). Time marks: 10 sec.

In two control cats under chloralose anaesthesia with open chest and under artificial respiration, the pressor action of the three doses of noradrenaline was entirely abolished by phenoxybenzamine (10 mg/kg i.v.).

The effect of noradrenaline on the blood pressure of pithed cats in which the cardiac sympathetic nerves were continuously stimulated

In two pithed cats previously injected with phenoxybenzamine (10 mg/kg i.v.), noradrenaline (0.125, 0.25 and 0.5 μg/kg) produced an average increase in arterial blood pressure of 22, 38 and 52 mm Hg respectively. The postganglionic cardiac sympathetic nerves were continuously stimulated under conditions such that the heart rates of the pithed cats were increased and maintained at 192 and 208 beats/min. This produced an increase in resting arterial blood pressure of 34 and 42 mm Hg respectively. When noradrenaline was injected under these conditions it failed to produce any further increase in blood pressure (Fig. 7). It would thus appear that in the pithed cat noradrenaline increases blood pressure by an action on the heart. If this were so the effect should be abolished by pronethalol which abolishes the cardiac chronotropic, and inotropic action of sympathomimetic amines (Black & Stephenson, 1962).

Effect of pronethalol on the pressor action of noradrenaline in pithed cats injected with phenoxybenzamine

In two pithed cats and in two chloralosed cats with sympathetically denervated hearts and previously injected with phenoxybenzamine (10 mg/kg i.v.) the increases in arterial blood pressure produced by noradrenaline (0.125, 0.25 and 0.5 μg/kg) were abolished by intravenous administration of pronethalol (2.5–4 mg/kg) (Fig. 8).

Cardiac output measurements

Direct evidence for the conclusion that noradrenaline increases blood pressure in pithed cats and in cats with sympathetically denervated hearts by an action on the heart was obtained in experiments in which the effect of noradrenaline on cardiac output was measured.

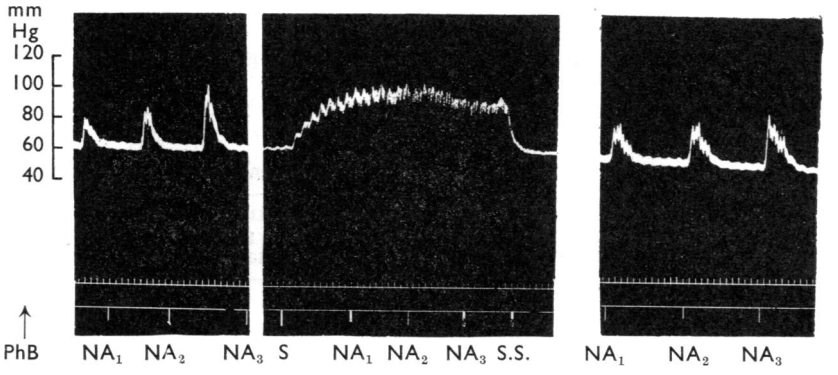

Fig. 7. Effect of continuous stimulation of the cardiac sympathetic nerves on the blood pressure response of a pithed cat (2.9 kg) treated with phenoxybenzamine (10 mg/kg), to intravenous injections of noradrenaline (NA_1, NA_2, NA_3, 0.125, 0.25 and 0.5 μg/kg resp.). Phenoxybenzamine was intravenously injected 30 min before the beginning of the experiment. At S, the right postganglionic cardiac sympathetic nerves were continuously stimulated with rectangular pulses of 0.5 msec duration, at a frequency of 5/sec and at strength of 6 v. S.S. stimulation of the sympathetics nerves stopped. Time marks: 30 sec.

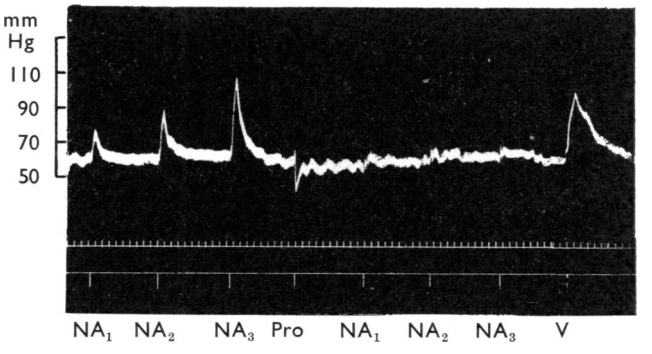

Fig. 8. Effect of intravenous injection of pronethalol (Pro 4 mg/kg) on the blood pressure response of a pithed cat (2.5 kg) treated with phenoxybenzamine (10 mg/kg), to intravenous injections of noradrenaline (NA_1, NA_2, NA_3, 0.125, 0.25 and 0.5 μg/kg resp.) and vasopressin (V, 0.1 mU). Phenoxybenzamine was intravenously administered 30 min before the beginning of the experiment. Time marks: 30 sec.

(*a*) *Anaesthetized cats.* In three chloralosed cats intravenous infusions of noradrenaline (0.375 and 0.75 μg/kg/min) raised the arterial blood pressure and caused a slowing of the heart. The cardiac output, however, remained unchanged. When the same doses of noradrenaline were infused 30 min after a dose of phenoxybenzamine (10 mg/kg i.v.) the pressor action of noradrenaline was abolished and although noradrenaline produced tachycardia, the cardiac output remained the same. (Table 6.)

(*b*) Spinal cats. The results were similar to those obtained in chloralosed cats except that the pressor action of noradrenaline was accompanied by tachycardia. Phenoxybenzamine (10 mg/kg i.v.) abolished the pressor action of noradrenaline without modifying its positive chronotropic effect. Noradrenaline did not increase cardiac output either before or after injecting phenoxybenzamine (Table 6).

TABLE 6

EFFECT OF NORADRENALINE ON THE ARTERIAL BLOOD PRESSURE, CARDIAC OUTPUT AND TOTAL PERIPHERAL RESISTANCE IN CATS UNDER DIFFERENT CONDITIONS

B.P.= Arterial blood pressure, mm Hg; C.O.= cardiac output, l./kg/min; P.R.= total peripheral resistance

Number of experiments and treatment	Before noradrenaline			Changes after noradrenaline: After infusing 0·375 μg/kg/min noradrenaline			Changes after noradrenaline: After infusing 0·75 μg/kg/min noradrenaline		
	B.P.	C.O.	P.R.	B.P.	C.O.	P.R.	B.P.	C.O.	P.R.
Two cats anaesthetized with chloralose	130	0·24	0·54	160	0·24	0·66	180	0·25	0·72
Ditto + phenoxybenzamine 10 mg/kg (i.v.)	85	0·22	0·38	85	0·22	0·38	85	0·21	0·4
Two spinal cats	90	0·21	0·43	126	0·20	0·60	149	0·20	0·70
Ditto + phenoxybenzamine 10 mg/kg (i.v.)	70	0·20	0·35	70	0·20	0·35	70	0·20	0·35

(*c*) *Pithed cats.* In contrast to the results of experiments on anaesthetized and on spinal cats, the increase in blood pressure produced by noradrenaline infusions in pithed cats was accompanied by an increase in cardiac output. When noradrenaline was injected in the presence of phenoxybenzamine 10 mg/kg i.v.) its pressor action was reduced by half but the increase in cardiac output was the same as before phenoxybenzamine (Table 7).

TABLE 7

EFFECT OF NORADRENALINE ON THE ARTERIAL BLOOD PRESSURE, CARDIAC OUTPUT AND TOTAL PERIPHERAL RESISTANCE IN CATS UNDER DIFFERENT CONDITIONS

B.P.= Arterial blood pressure, mm Hg; C.O.= cardiac output, l./kg/min; P.R.= total peripheral resistance

Number of experiments and treatment	Before noradrenaline			Changes after noradrenaline: After infusing 0·375 μg/kg/min noradrenaline (i.v.)			Changes after noradrenaline: After infusing 0·75 μg/kg/min noradrenaline (i.v.)		
	B.P.	C.O.	P.R.	B.P.	C.O.	P.R.	B.P.	C.O.	P.R.
Two pithed cats	60	0·16	0·37	110	0·20	0·55	154	0·24	0·64
Ditto + phenoxybenzamine 10 mg/kg (i.v.)	65	0·19	0·34	95	0·27	0·35	117	0·30	0·35
Two chloralosed cats with symp. denerv. hearts	80	0·15	0·53	128	0·21	0·60	164	0·25	0·65
Ditto + phenoxybenzamine 10 mg/kg (i.v.)	55	0·16	0·30	81	0·26	0·30	102	0·33	0·31

(*d*) *Anaesthetized cats with sympathetically denervated hearts.* In anaesthetized cats with sympathetically denervated hearts the increase in blood pressure produced by infusions of noradrenaline was due to an increase in cardiac output as well as due to an increase in peripheral resistance. The remaining pressor action of noradrenaline after injecting phenoxybenzamine (10 mg/kg i.v.) can be accounted for by the increase in cardiac output (Table 7).

DISCUSSION

In the present investigation it was demonstrated that phenoxybenzamine 10 mg/kg) and phentolamine (2 mg/kg) abolish the pressor effect of noradrenaline in anaesthetized cats and in spinal cats. In the pithed cat, however, these drugs reduce the effect of noradrenaline but do not abolish it.

Drugs which specifically abolish the pressor action of noradrenaline are also known to antagonize its vasoconstrictor action in skeletal muscle and in the vascular beds of the splanchnic area, skin, kidney and the head (Folkow, Frost & Uvnas, 1948; Johnson, Green & Lanier, 1953; Green, Denison, Williams, Carvey & Tabor, 1954; Green, Macleod, Anderson & Denison, 1954; Green, Deal, Bardhanabaedya & Denison, 1955; Deal & Green, 1956; Butterworth, 1963). The results of the present experiments show that phenoxybenzamine and phentolamine also abolish the vasoconstrictor action of noradrenaline in the femoral and splanchnic vascular beds in anaesthetized or in pithed cats. Hence the rise in arterial blood pressure produced by noradrenaline in the pithed cat in the presence of phenoxybenzamine or phentolamine would appear to be due to a mechanism other than vasoconstriction.

Ekstein & Hosley (1961) and Zimmermann, Brody & Beck (1960) have shown that removal of the sympathetic tone to the heart causes a reduction in heart rate, cardiac output and ventricular work. Since noradrenaline is considered to be the sympathetic transmitter, injection of this amine under these conditions would be expected to restore temporarily the cardiac sympathetic tone and to increase the rate and output of the heart. In anaesthetized cats with sympathetically denervated hearts, when the vasoconstrictor action of noradrenaline is blocked by phenoxybenzamine, noradrenaline still produces an increase in blood pressure. It is therefore conceivable that in pithed cats, because of the loss of cardiac sympathetic tone, noradrenaline increases the blood pressure by an action on the heart. This hypothesis is supported by the findings that in the pithed cat treated with phenoxybenzamine, and subjected to continuous stimulation of the cardiac sympathetic nerves in an attempt to restore the tone of the heart, doses of noradrenaline did not increase arterial blood pressure.

It is interesting to compare the results with those of Withrington & Zaimis (1961) in reserpine treated cats. According to these authors a dose of phenoxybenzamine large enough to abolish in the normal cat the vasoconstrictor action of noradrenaline failed to reduce the pressor action of noradrenaline in reserpine treated cats. These authors consider that 24 hr after the administration of reserpine (1 mg/kg) blood pressure changes in response to injected noradrenaline are secondary to changes in the contraction of the heart muscle. Although they explain these findings by saying that the heart of the reserpine treated cat is in failure an alternative explanation is possible. Reserpine is known to deplete noradrenaline from sympathetic nerves and from tissue stores (Bertler, Carlsson & Rosengreen, 1956; Burn & Rand, 1958) and therefore a reserpine treated cat is in fact functionally sympathectomized. It can, therefore, be argued that noradrenaline increases arterial blood pressure in reserpine pretreated cats by temporarily restoring the cardiac sympathetic tone.

In the pithed cat and in the anaesthetized cat in which the heart has been sympathetically denervated, the rise in blood pressure produced by noradrenaline is due to an action

on the heart. This is demonstrated by the observation that this effect is abolished by pronethalol, which is known to antagonize the cardiac positive chronotrophic and inotropic actions of noradrenaline and other catechol amines Black & Stephenson, 1962).

Cardiac output studies have also demonstrated that whereas the increase in blood pressure produced by noradrenaline in anaesthetized cats is due solely to an increase in total peripheral resistance this is not so in pithed cats. In the pithed cat noradrenaline raises arterial blood pressure by increasing total peripheral resistance as well as by increasing cardiac output. The pressor action of noradrenaline in pithed cats injected with phenoxybenzamine is due entirely to an increase in cardiac output.

The increase in sensitivity of pithed cats to noradrenaline can also be explained on the basis of the findings that in such an animal noradrenaline increases arterial blood pressure by increasing peripheral resistance as well as cardiac output. Lockett (1950) has shown that in dogs thoracic and lumbar sympathectomy potentiated the pressor responses to noradrenaline ; potentiation of the pressor action of noradrenaline by ganglion blocking drugs has also been demonstrated (Page & Taylor, 1950 ; Paton, 1951 ; Bartorelli, Capri & Cavalca, 1954). Karim (1965) has shown that the potentiation of the pressor action of noradrenaline in spinal cats by hexamethonium, bretylium and procaine, all of which depress sympathetic tone, is accompanied by an increase in cardiac output, without any significant change in total peripheral resistance.

It is difficult to explain why noradrenaline does not increase cardiac output in animals with intact sympathetic innervation. The suggestion that noradrenaline fails to increase cardiac output in such an animal because of the reflex slowing accompanying the pressor action of noradrenaline, cannot be true since noradrenaline did not increase the cardiac output in spinal cats. The cardiac sympathetic tone in the spinal cat is not abolished since a reduction in heart rate occurs when the cardiac sympathetic nerves in such an animal are cut. Sympathetically innervated hearts have been shown to behave in a manner different to that of denervated hearts. Thus according to Eckstein *et al.* (1961) in the presence of intact sympathetic pathways the heart fails to increase its rate and output when atrial pressure is increased. After denervation the heart (*in vivo*) increases its rate and output when the atrial pressure is increased.

SUMMARY

1. Phenoxybenzamine and phentolamine abolish the increase in arterial blood pressure produced by noradrenaline in anaesthetized and in spinal cats. In pithed cats, however, phenoxybenzamine and phentolamine reduce, but do not abolish, the pressor action of noradrenaline.

2. Measurements of the cardiac output and blood flow have led to the conclusion that whereas in the anaesthetized cat the pressor action of noradrenaline is due solely to an increase in total peripheral resistance, in the pithed cat noradrenaline raises the blood pressure by increasing cardiac output as well.

3. The pressor action of noradrenaline in pithed cats injected with phenoxybenzamine and phentolamine is due entirely to an increase in cardiac output.

4. Evidence is presented to suggest that in the pithed cat, because of the loss of cardiac sympathetic tone, noradrenaline raises the blood pressure by an action on the heart.

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