

The inactivation of noradrenaline and isoprenaline in dogs

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Summary

1. The removal of infused noradrenaline and isoprenaline from the circulation of the dog has been studied, using the blood-bathed organ technique.
2. Both catecholamines were removed in peripheral vascular beds; in all organs studied, noradrenaline was removed to a greater degree than isoprenaline.
3. The hind legs removed an average of 60% of the noradrenaline passing through, but only 34% of the isoprenaline. With noradrenaline, the degree of removal *decreased* as the concentration increased, but with isoprenaline, the degree of removal *increased* with concentration.
4. After phenoxybenzamine, the proportion of isoprenaline removed was unchanged, whereas that of noradrenaline was decreased. The change in removal with the concentration of noradrenaline was also abolished.
5. The results are consistent with the concept that a small fraction of infused noradrenaline is removed from the circulation by Uptake₁ and that this is blocked by phenoxybenzamine. Isoprenaline, and the rest of the noradrenaline, are removed by another process (Uptake₂?) followed by intracellular metabolism. This inactivation process is unaffected by phenoxybenzamine in concentrations sufficient to give α -adrenoceptor blockade.
6. After isoprenaline infusions, a substance sometimes appeared in the circulation which contracted the blood-bathed organs.
7. The systemic pressure response to vaso-active hormones is not a reliable indicator of the concentration of hormone in the arterial circulation.

Introduction

When adrenaline or noradrenaline are infused intravenously they have a half-life in the circulation of less than one circulation time (Ferreira & Vane, 1967). The pulmonary circulation removes about 20% of an infusion of noradrenaline, but there is no removal of adrenaline at this site (Ginn & Vane, 1968). However, both catecholamines disappear in peripheral vascular beds. Celander & Mellander (1955) studied the disappearance of adrenaline and noradrenaline in the vascular beds of the cat; they found that up to 90% of an arterial infusion of catecholamine dis-

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appeared in the hindquarters. Similar results were obtained in the spleen, kidneys and intestine. Vane (1966) and Ginn & Vane (1968) confirmed these results and extended them to the dog: they found more than 80% of an infusion of adrenaline or noradrenaline into the hindquarters was constantly removed in one passage through this vascular bed, even though the infusion was maintained for 20 min or more.

Termination of the actions of catecholamines may be by metabolism, by uptake or by both. It has been suggested (Vane, 1969; Lightman & Iversen, 1969) that extra-neuronal uptake (Uptake₂) may play some role in the rapid removal of circulating catecholamines. Whereas noradrenaline is a good substrate for both Uptake₁ and Uptake₂, isoprenaline is only a substrate for Uptake₂ (Callingham & Burgen, 1966). We have, therefore, measured the disappearance of noradrenaline and isoprenaline in different vascular beds of dogs and in addition have studied the influence of phenoxybenzamine on this removal process.

Methods

The blood-bathed organ technique (Vane, 1964) was used to assay catecholamines in the circulation. A rat stomach strip (Vane, 1957) and a chick rectum (Mann & West, 1950) were superfused (Gaddum, 1953) in cascade with Krebs solution at 37° C oxygenated with 5% carbon dioxide in oxygen whilst the dog was being prepared. The movements of the assay organs were recorded on a kymograph with auxotonic levers (Paton, 1957) of 16 to 1 magnification with an initial load on the tissues of 1–3 g.

Twenty-six mongrel dogs of either sex weighing 7–25 kg were anaesthetized with halothane: anaesthesia was then maintained with chloralose (100 mg/kg intravenously) with additional pentobarbitone sodium (1–5 mg/kg subcutaneously or intramuscularly) when required. The trachea was cannulated and artificial respiration was maintained. Polyethylene cannulae were tied into the left femoral artery and femoral vein for the removal and replacement of blood. Mean arterial blood pressure was recorded on the kymograph by a mercury manometer attached to the side arm of the arterial cannula.

The blood for superfusion of the isolated assay organs was pumped either from the femoral arterial cannula or from just above the aortic valves at a constant rate of 10–15 ml/min. The blood from the ascending aorta was obtained from the inner tube of a coaxial catheter (Ferreira & Vane, 1967) passed down the right carotid artery until the catheter lay in the left ventricle. It was then withdrawn until the change in the pulse pressure recorded through it showed that it was just above the aortic valves. The outer tubing of the coaxial catheter was about 1 cm shorter and the drugs were infused through this tube; thus the infused drug mixed with the total cardiac output and circulated once through the peripheral vascular beds before being assayed in the blood taken from the inner catheter. After the blood had superfused the assay tissues it was collected in a reservoir and returned by gravity into the left femoral vein. The disappearance of noradrenaline, isoprenaline (and occasionally adrenaline) was measured by comparing the responses of the superfused assay tissues induced by intravenous infusions with those induced by intra-arterial infusions of catecholamines.

For intra-arterial administration, the catecholamines were infused at three sites: (1) through the coaxial catheter into the ascending aorta to measure the removal of catecholamines in one circulation through the whole body; (2) through a catheter introduced retrogradely into the femoral artery. The tip of the catheter was in the abdominal aorta just above the iliac bifurcation. These infusions reached the hindquarters; (3) through the same catheter pushed up the abdominal aorta so that the tip was above the renal arteries. These infusions reached the kidneys, the lower parts of the body and sometimes, when the tip of the catheter was above the coeliac axis, the abdominal viscera as well. Each position of the catheter in the aorta was checked by marking the catheter and exposing the aorta at the end of the experiment.

In four dogs the hindquarters were perfused with a constant outflow pump (Harvard peristaltic pump, model 500-1200 M). Blood was taken from a cannula in the aorta below the renal arteries and pumped into the hindquarters through a second aortic cannula above the iliac bifurcation. The mean perfusion pressure and mean carotid blood pressure were registered by separate mercury manometers ($1 \text{ mmHg} \equiv 1.333 \text{ mbar}$) and the perfusion pressure was adjusted to be a little above the level of the mean blood pressure: this gave a constant rate of flow through the hindquarters of between 50–80 ml/min. Removal of catecholamines in the perfused hindquarters was measured by assay tissues bathed in mixed venous blood taken from the right atrium or in carotid arterial blood. The effects on them of intra-arterial infusions as the blood entered the iliac bifurcation were compared with the effects of infusions into the femoral vein.

In all experiments the dogs were given heparin (1,000 i.u./kg) intravenously before external circulation of blood was started. Other drugs used were (–)-adrenaline bitartrate (British Drug Houses); (–)-noradrenaline bitartrate (Sigma); (\pm)-isoprenaline sulphate (Boots) and phenoxybenzamine hydrochloride (Smith Kline & French). The doses of the catecholamines are expressed as base.

Results

In all the vascular beds studied noradrenaline was removed to a greater degree than isoprenaline: this was seen best in the hindquarters (Table 1). From infusions of noradrenaline [(0.5–8.5 $\mu\text{g}/\text{kg}$)/min] into the hindquarters there was an average disappearance of 61%. From isoprenaline infusions [(0.04–1.7 $\mu\text{g}/\text{kg}$)/min] there was an average disappearance of 34%. Figure 1 shows an experiment in which noradrenaline was infused at different sites into the aorta. An infusion of noradrenaline (160 $\mu\text{g}/\text{min}$) had to be given into the aorta close to the kidneys in order to obtain a carotid blood concentration equivalent to that produced by 20 $\mu\text{g}/\text{min}$ intravenously. Less noradrenaline was removed from infusions into the hindquarters.

There are several interesting points which are illustrated by these experiments. First, when the infusion catheter was near the origin of the renal vessels, more of the infused noradrenaline disappeared than when the catheter was higher up the aorta (at points c and d, Fig. 1). This must mean that the infusion was differently distributed when made near the kidneys, presumably through streamlined flow directly into the renal arteries. Second, there is no correlation between the size of the blood pressure response and the amount of noradrenaline removed. For instance, with almost complete removal in the kidneys, as shown by infusions at

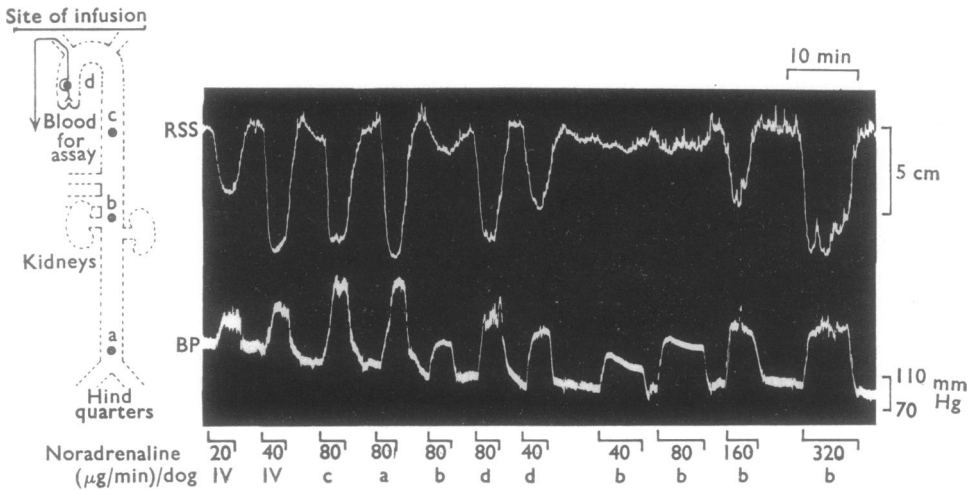


FIG. 1. Dog (12 kg, male) anaesthetized with chloralose. The removal of noradrenaline (NA) by different vascular beds. Upper tracing, a rat stomach strip (RSS) superfused with the arterial blood taken from the root of the aorta through the inner tubing of the coaxial catheter tied in the right carotid artery. Lower tracing, mean blood pressure (BP) registered by the mercury manometer in the left femoral artery. NA [(20–320 $\mu\text{g}/\text{min}/\text{dog}$)] was infused intravenously into the left femoral vein (IV) or intra-arterially at different sites. Intra-arterial infusions of NA were made through a catheter pushed up retrogradely from the left femoral artery to (a, b, c) or through the outer tubing of the coaxial catheter (d). The sites of the infusions of NA are shown on the diagram. The tracing shows that from an infusion of NA (80 $\mu\text{g}/\text{min}$) to the hindquarters (a) 40% disappeared. From an infusion of NA (80 $\mu\text{g}/\text{min}$) at the level of the right renal artery (b) 90% disappeared. From an infusion of NA (80 $\mu\text{g}/\text{min}$) into the ascending aorta (d) 60% disappeared. From an infusion of NA (80 $\mu\text{g}/\text{min}$) into the thoracic aorta (c) 55% disappeared. Even with as high an infusion rate as 320 $\mu\text{g}/\text{min}$ at (b), about 80% was abstracted. Time, min; vertical scales, cm and mmHg.

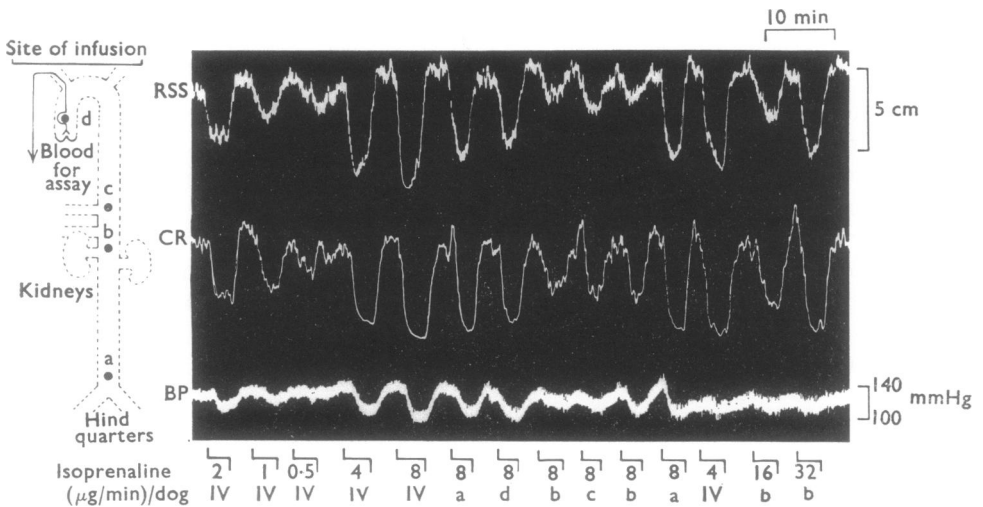


FIG. 2. Dog (15 kg, male) anaesthetized with chloralose. The removal of isoprenaline (IP) by different vascular beds. The experiment was as in Fig. 1. Upper tracing, a rat stomach strip (RSS); middle tracing, a chick rectum (CR) superfused with arterial blood. Lower tracing, the mean arterial blood pressure (BP). IP (0.5–32 $\mu\text{g}/\text{min}$) was infused intravenously (IV) or intra-arterially at sites a, b, c, d. At a rate of 8 $\mu\text{g}/\text{min}$, there was a loss of isoprenaline of 50% at (a), 90% at (b), 80% at (c) and 60% at (d). Even at an infusion rate of 32 $\mu\text{g}/\text{min}$ there was still a loss of 90% at (b). Time, min; vertical scales, cm and mmHg.

TABLE 1. Removal of noradrenaline (NA) and isoprenaline (IP) from the circulation by different vascular beds

Infusion into	Catecholamine	Number of dogs	Number of estimations	Mean dose and range of doses [$\mu\text{g}/\text{kg}/\text{min}$]	Mean removal \pm S.E.M. (%)	Correlation between dose and removal	Difference in removal between NA and IP
Ascending aorta (total cardiac output)	NA	9	18	3.3 (1.1-6.8)	55.3 \pm 2.29	None	$t=2.53$
	IP	10	25	0.7 (0.1-2.2)	47.6 \pm 2.06	None	0.01 $< P < 0.05$
Viscera, kidneys and hindquarters	NA	8	17	5.5 (0.9-27.2)	93.7 \pm 1.55	None	$t=2.74$
	IP	11	24	1.4 (0.1-4.0)	87.8 \pm 1.37	None	0.01 $< P < 0.05$
Hindquarters	NA	10	19	2.3 (0.5-8.5)	60.7 \pm 3.38	$r = -0.6125$	$t=5.42$
	IP	13	24	0.5 (0.04-1.7)	33.5 \pm 3.70	0.05 $< P < 0.1$	$P < 0.001$

r , Correlation coefficient.

TABLE 2. Influence of phenoxybenzamine (2-6 mg/kg) on the removal of noradrenaline (NA) and isoprenaline (IP) by different vascular beds

Infusion into	Catechol-amine	Number of dogs	Number of estimations	Mean dose and range of doses [$\mu\text{g}/\text{kg}/\text{min}$]	Mean removal \pm S.E.M. after phenoxybenzamine (%)	Difference in removal of NA or IP between treated and untreated dogs
Ascending aorta (total cardiac output)	NA	4	11	3.9 (1.4-8.0)	22.4 \pm 6.00	$t=6.19$ $P < 0.001$
	IP	3	9	0.5 (0.2-0.7)	52.2 \pm 5.02	$t=1.01$ $P > 0.1$
Viscera, kidneys and hindquarters	NA	4	8	4.3 (1.8-8.0)	71.4 \pm 5.88	$t=5.11$ $P < 0.001$
	IP	2	6	1.3 (0.5-2.2)	86.0 \pm 2.13	$t=0.89$ $P > 0.1$
Hindquarters	NA	5	15	2.7 (0.7-8.3)	32.7 \pm 2.92	$t=6.35$ $P < 0.001$
	IP	3	5	1.1 (0.02-4.7)	34.2 \pm 6.90	$t=0.09$ $P > 0.1$

point b, there was still a substantial blood pressure rise, presumably because of the direct effects of noradrenaline on renal vessels at a point before removal occurred.

An experiment with isoprenaline (Fig. 2) shows essentially similar features. There was a greater loss of isoprenaline from infusions made close to the renal arteries (point b) than from infusions made into the ascending aorta. There was also a lack of correlation between the fall in blood pressure and the amount of isoprenaline which survived passage through a vascular bed.

The results of individual infusions at various dose levels in different experiments are shown graphically in Fig. 3. Each point represents a separate observation. There was about 50% removal of both noradrenaline and isoprenaline infused into the ascending aorta and this did not change with the rate of infusion. When infused near the kidneys there was a 75–95% removal and this was also independent of the rate of infusion. With infusions into the hindquarters, however, at the higher rates there was a greater removal of isoprenaline and a smaller removal of noradrenaline.

Since noradrenaline is vasoconstrictor and isoprenaline vasodilator, the removal process might have been influenced by the rate of blood flow. Figure 4 is a tracing from an experiment in which the hindquarters of a dog were perfused at constant blood flow. For infusions of noradrenaline, at rates of 8 μg or 16 $\mu\text{g}/\text{min}$, the disappearance in the hindquarters was 50%. For infusions of isoprenaline, there was 30% removal from a rate of 1 $\mu\text{g}/\text{min}$ and 50% removal from a rate of 2 $\mu\text{g}/\text{min}$. After the intra-arterial infusions of isoprenaline had stopped, the rate

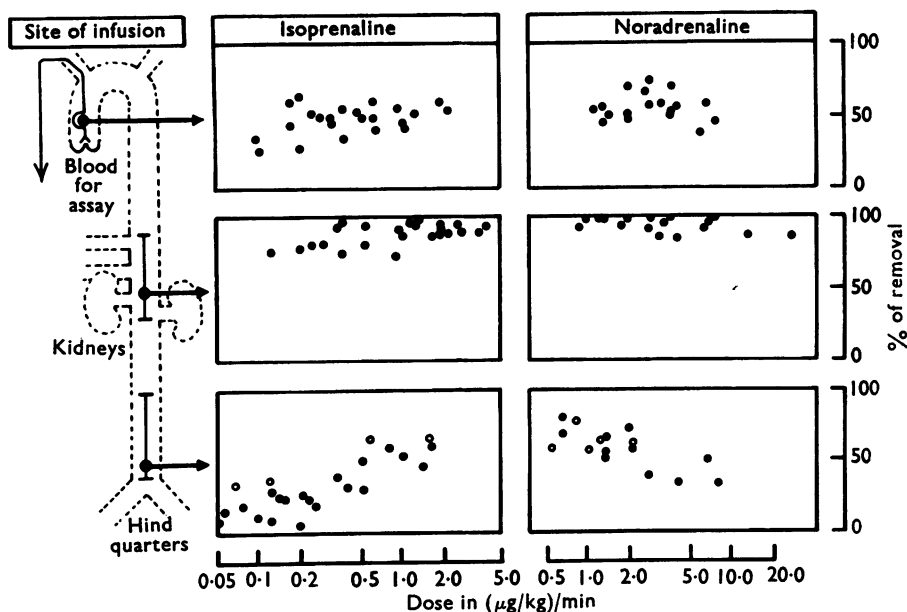


FIG. 3. Disappearance of isoprenaline and noradrenaline from infusions at different sites in the dog. The diagram shows the sites of catecholamine infusions and the arrows indicate the corresponding graphs for whole body (upper), kidney and viscera (middle) and hind-quarters (lower). Each dot represents a single estimation. Open circles are for the four experiments with perfused hindquarters. Ordinate, % of removal; abscissa, log scale of the infused rates of catecholamines, expressed as ($\mu\text{g}/\text{kg}$)/min.

of recovery of the assay tissues was somewhat slower than after the intravenous infusions. This tracing also shows that 65% of an infusion of adrenaline was removed in the hindquarters.

Effects of phenoxybenzamine

Phenoxybenzamine was injected intravenously in doses (2–6 mg/kg) sufficient to abolish the pressor effects of noradrenaline. The phenoxybenzamine relaxed the assay organs and their sensitivity to catecholamines was diminished. However,

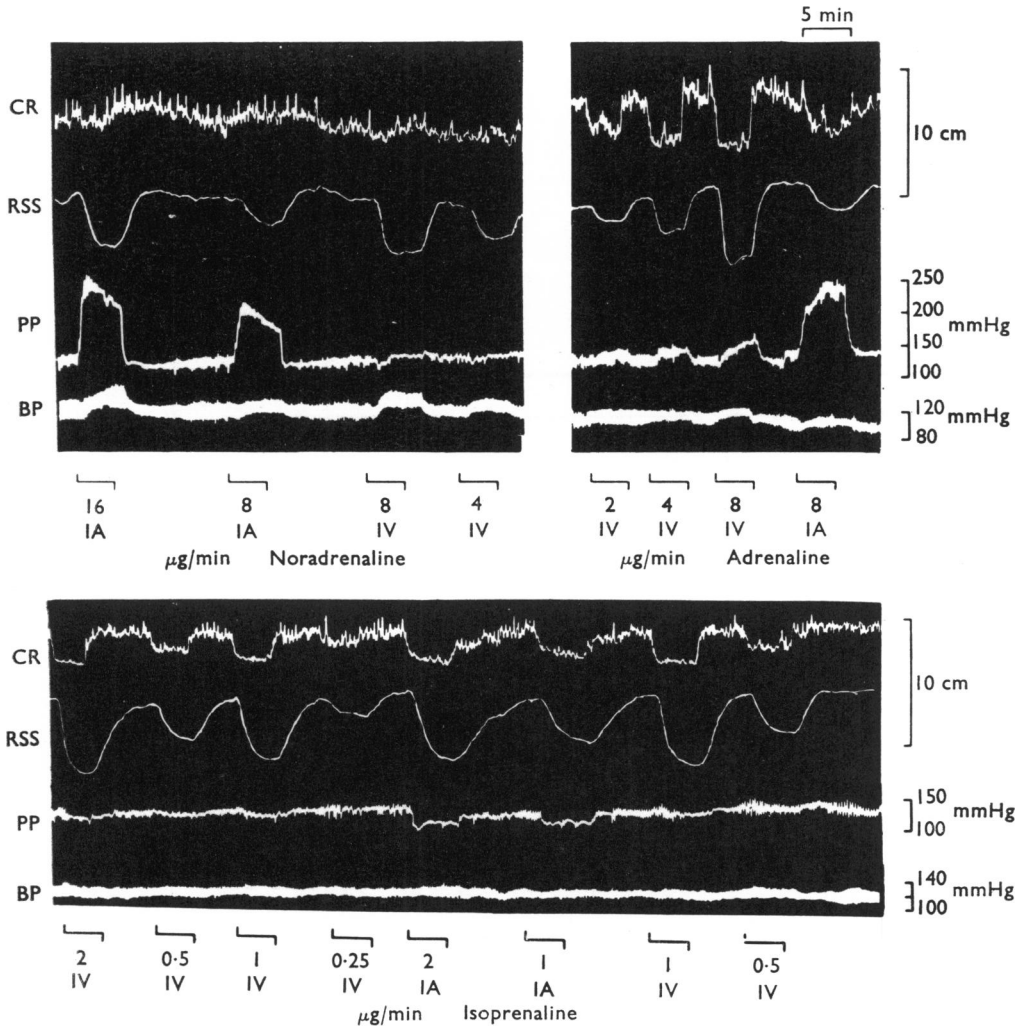


FIG. 4. Tracings taken from an experiment in which the hindquarters of an anaesthetized dog (15 kg, male) were perfused with a constant flow pump. Each section shows (top to bottom) the movements of a chick rectum (CR) and rat stomach strip (RSS) bathed in carotid arterial blood, the perfusion pressure (PP) and the blood pressure (BP). Top left: Intra-arterial infusions of noradrenaline (16 and 8 $\mu\text{g}/\text{min}$) caused large increases in PP. The RSS shows that 50% of each infused dose disappeared. Top right: from an intra-arterial infusion of adrenaline (8 $\mu\text{g}/\text{min}$) about 65% disappeared. The bottom tracing shows that 30% disappeared from an isoprenaline infusion of 1 $\mu\text{g}/\text{min}$ and 50% from an infusion of 2 $\mu\text{g}/\text{min}$. Note also the relatively slow recovery of the blood-bathed organs after the intra-arterial infusions. Time, min; vertical scales cm and mmHg.

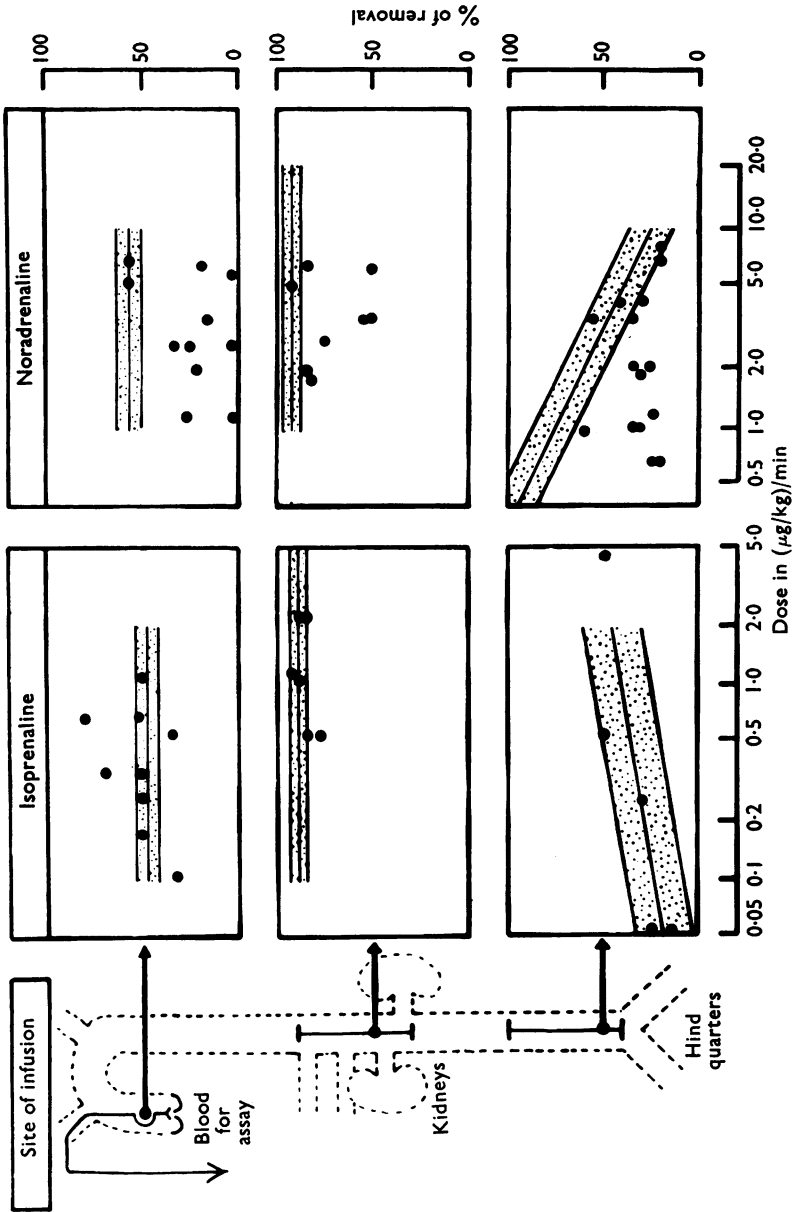


FIG. 5. Influence of phenoxybenzamine on the removal of catecholamines by different vascular beds. The figure is similar to Fig. 3. The closed circles show each observation obtained in twelve dogs pretreated with phenoxybenzamine (2-6 mg/kg). The dotted strips show the mean removal of catecholamines $\pm 2 \times$ S.E. in normal dogs, taken from Fig. 3 and Table 2.

it was still possible to estimate the amounts of catecholamine removed from the circulation; this was done 1–2 h after injection of phenoxybenzamine. The results are summarized in Table 2 and Fig. 5. There was no alteration in the removal of isoprenaline after phenoxybenzamine, but at all three sites of infusion the removal of noradrenaline was reduced. Thus, the average removal of noradrenaline from infusions into the total arterial bed was reduced from 55% to 22%, from infusions to the viscera from 93% to 71% and from infusions to the hindquarters from 61% to 33%.

An interesting feature of the change in removal in the hindquarters was the abolition of the dose-dependence (Fig. 5). Whereas before phenoxybenzamine the percentage removal of noradrenaline decreased as the rate of infusion increased, after phenoxybenzamine the removal became independent of the infusion rate.

Appearance of uncharacterized substance after isoprenaline infusions

Occasionally the assay tissues did not maintain a relaxation for the whole duration of an isoprenaline infusion. Furthermore, when an infusion was stopped the

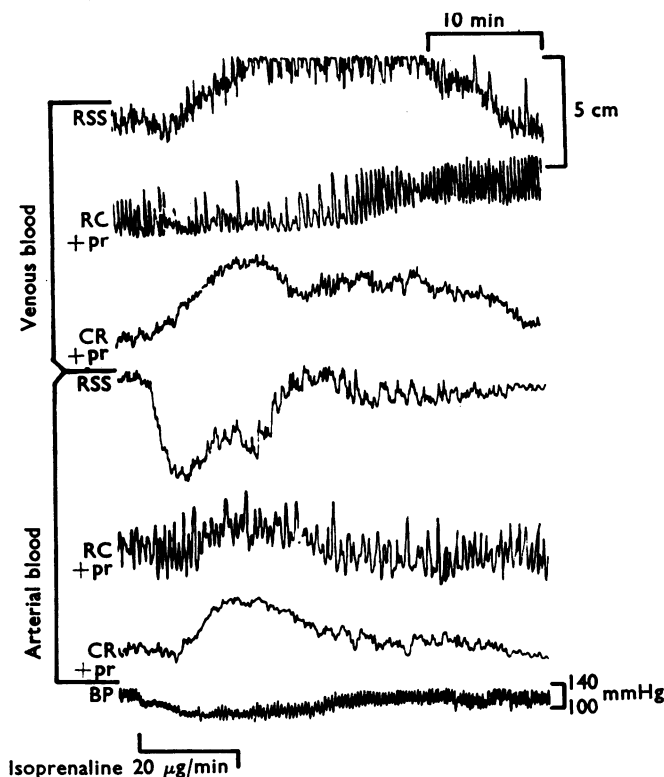


FIG. 6. Dog (18 kg, male) anaesthetized with chloralose. The assay tissues were a rat stomach strip (RSS), a rat colon (RC) and chick rectum (CR) all bathed in venous blood and a similar set bathed in arterial blood. Propranolol was perfused through the lumens of the rat colons (RC+pr) and chick rectums (CR+pr). The bottom tracing is of mean blood pressure (BP). When isoprenaline (20 µg/min) was infused into the abdominal aorta, some of it recirculated and relaxed the RSS in arterial blood. However, the CRs and the RSS in venous blood contracted, showing the presence of a different circulating substance. When isoprenaline (50 ng/ml) was infused directly to the assay tissues, there was no effect on those blocked with propranolol, but both the RSSs relaxed. Time, min; vertical scales cm and mmHg.

relaxation sometimes gave way to an after-contraction above the baseline. These effects suggested that a substance which contracted the assay tissues was sometimes being detected in the circulation during and after the isoprenaline infusions. To test this possibility, two banks of assay tissues were superfused with blood from a dog; their movements were detected by Harvard smooth muscle transducers and recorded on an 8-channel dynograph. One bank was superfused with mixed venous blood taken from the right atrium through a catheter in the right jugular vein; the other was superfused with arterial blood taken from the right carotid artery. The relaxant actions of catecholamines on the rat colon and chick rectum, which are predominantly β -effects, were abolished by intra-luminal infusions of propranolol (1.0 mg/ml; 0.1 ml/min; Hodge, Lowe & Vane, 1966). Figure 6 shows that when isoprenaline (20 μ g/min) was infused through a catheter into the ascending aorta, a substance appeared in the circulation which contracted the rat stomach strip and chick rectum bathed in venous blood and also the rat colon and chick rectum bathed in arterial blood. The rat stomach strip bathed in arterial blood was not treated with propranolol, so that it relaxed to the isoprenaline which re-circulated. However, the relaxation was not maintained, presumably because of the appearance of the contractor substance. The appearance of this contractor substance in the circulation was capricious. In some experiments (23%) it could not be detected; in others (42%) it only appeared on the first and second infusions of isoprenaline. In the remaining 35% it was continuously released during each infusion of isoprenaline.

Discussion

In the mouse with doses of noradrenaline ranging from 3–10 μ g/kg, Iversen & Whitby (1962) found that 55% of the injected dose was retained unchanged in the tissues 30 min after the injection. Our results of infusions into the total cardiac output of the dog also show that 55% of the infused dose was removed in one passage through the peripheral vascular beds. However, the experiments of Iversen & Whitby (1962) were with single injections whereas we have used continuous infusions. Thus, if the 55% removal of noradrenaline that we find represents an uptake process the cells involved must have a large storage or metabolic capacity.

The processes which remove isoprenaline and noradrenaline from the circulation of the dog seem to have the following characteristics:

(1) They vary from vascular bed to vascular bed; thus when the infusions reached the kidney and viscera, there was a very much larger removal than when they reached only the hindquarters.

(2) Equilibrium conditions are reached remarkably quickly. Within 2–3 min of the start of an infusion both the effects on the vasculature and the overflow of catecholamines into the venous circulation were constant. They then remained constant for as long as the infusion was maintained (up to 30 min). Thus the catecholamine filled the extra-cellular space available to it and came into equilibrium with extra- and intra-cellular removal processes within 2–3 min.

(3) There was no evidence for slow leakage of noradrenaline back into the circulation in an active form after it had been removed by a particular vascular bed. Thus the relaxations of the isolated blood-bathed organs after an intra-arterial infusion recovered back to base line at approximately the same speed as after an intravenous infusion. For isoprenaline, there was a relatively slower

recovery of the assay tissues after an intra-arterial infusion into the hindquarters than after an intravenous one (see Fig. 4). This suggests that some of the isoprenaline which had been removed was leaking back in an active form into the circulation.

Lightman & Iversen (1969) have concluded that Uptake₂ in the rat heart is not a threshold phenomenon but operates at all concentrations of catecholamine. Phenoxybenzamine is a potent inhibitor of neuronal uptake of noradrenaline (Iversen & Langer, 1969) and of Uptake₂ *in vitro* (Lightman & Iversen, 1969). By contrasting the removal of isoprenaline (which is not a substrate for Uptake₁) with that of noradrenaline before and after phenoxybenzamine, we had hoped to provide evidence for or against Uptake₂ as the process responsible for rapid termination of catecholamine effects *in vivo*. The decrease in the disappearance of noradrenaline which we observed as the dosage increased suggests that some mechanism was being saturated. Uptake₁ saturates at concentrations above 0.5 $\mu\text{g/ml}$; with a hind-quarter bloodflow of about (5 ml/kg)/min, this concentration would be achieved by infusions of (2.5 $\mu\text{g/kg}$)/min. Thus, our results could be interpreted to mean that the greater disappearance of noradrenaline at the lower infusion rates was due to Uptake₁. The fact that the greater disappearance at lower infusion rates was not seen either with isoprenaline or with noradrenaline after phenoxybenzamine is consistent with this interpretation. However, there is also the possibility that the change in degree of disappearance is linked with the change in bloodflow induced by noradrenaline. We do not have enough results on this point, but in one experiment, in which bloodflow to the hindquarters was maintained at a constant rate, there was no difference in the removal of noradrenaline when given at different infusion rates, although the increased removal of isoprenaline at the higher infusion rate was still evident.

In the presence of sufficient phenoxybenzamine to abolish the α -adrenoceptor effects of noradrenaline, the removal of noradrenaline was reduced, but it was still substantial (up to 50%). Furthermore, the removal of isoprenaline was unaffected. These results suggest, first, that phenoxybenzamine blocks only Uptake₁ *in vivo* and, second, that only a fraction of circulating noradrenaline is removed by Uptake₁ *in vivo*.

Our results are consistent with the view that Uptake₂, followed by intra-cellular metabolism rather than storage, is a primary mechanism for removal of noradrenaline and isoprenaline from the circulation.

Three other points deserve mention. First, the occasional detection after isoprenaline infusions of a substance which contracted the chick rectum and rat stomach strip was of interest. This uncharacterized substance may be a metabolite of isoprenaline, to which the assay tissues are sometimes sensitive, or a substance sometimes released from another source. Further experiments are needed.

Second, when infusions were made near to the renal arteries there was much greater removal of the catecholamines from the circulation than when they were made into the hindquarters or in the ascending aorta. This observation suggests that the infusions in the region of the kidneys were being mainly directed by flow patterns into one of the major blood vessels such as the renal artery. Infusions made at this point therefore may not mix completely with the total blood flowing past.

Lastly, "the systemic pressor response technique" (Biron, 1968) has been used to estimate the removal of substances from the circulation. This technique depends on injecting the substance into a particular vascular bed and assuming that the blood pressure response produced is a result only of that proportion of the substance which re-circulates. Our experiments show quite clearly that, for infusions at least, this assumption is not valid. When infused intra-arterially both the vasoconstrictor substance noradrenaline, and the vasodilator isoprenaline, gave blood pressure responses which were not indicative of the amount of substance re-circulating, as shown by the blood-bathed organs. When a drug is injected intra-arterially to a particular vascular bed, the resultant change in blood pressure is a complex of many different factors. The drug first has a direct action on the injected vascular bed, which must sometimes affect the general blood pressure and summate with the general blood pressure response produced by that part of the injected drug which escapes and re-circulates. The relatively high concentration of the arterially-injected drug may also initiate local or general compensatory reflexes, changes in autoregulation or secretion of other vaso-active substances; any one of these factors may further modify the blood pressure response. Thus, although the "systemic blood pressure response" has the attraction of simplicity, it probably gives an erroneous estimate of the amount of substance removed by the particular vascular bed. This may apply particularly in organs with a high blood flow such as the lungs or the kidney, where local vasoconstriction or vasodilatation will have a pronounced effect on the blood pressure.

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