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THE CONTRIBUTION OF THE ARTERIAL CHEMORECEPTORS TO THE STIMULATION OF RESPIRATION BY ADRENALINE AND NORADRENALINE IN THE CAT

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SUMMARY

1. Intravenous infusions of adrenaline and noradrenaline in doses averaging 0·8 μg/kg.min increased the respiratory minute volume of anaesthetized cats breathing room air. The mean increase in respiratory minute volume was 14% during adrenaline infusion and 8% during noradrenaline infusion.

2. In a small group of decerebrate cats infusions of adrenaline and noradrenaline increased ventilation by 19 and 27% respectively.

3. Intravenous catecholamine infusions also increased the respiratory responses of anaesthetized animals to the inhalation of 5% or 10% O_2 in N_2 and to the inhalation of 5% CO_2 in air.

4. Adrenaline and noradrenaline infusions had no significant effect on the ventilation of animals breathing 100% O_2, nor did they significantly alter the respiratory response to the inhalation of 5% CO_2 in O_2.

5. After section of the carotid sinus and aortic nerves, a blood-pressure compensator being used to minimize changes in arterial pressure, catecholamines had no effect on the respiration of cats breathing air.

6. An increase in carotid body chemoreceptor discharge accompanied the increase in ventilation during catecholamine infusion.

7. Intravenous catecholamine infusions still produced an increase in ventilation and carotid body chemoreceptor discharge after both aortic nerves and both cervical sympathetic nerves had been cut.

8. Intra-arterial infusions into one carotid artery of 0·2 μg/kg.min of adrenaline or 0·1 μg/kg.min of noradrenaline led to mean increases in respiratory minute volume of 9·9 and 11·5% respectively. No increase occurred after section of the corresponding carotid sinus nerve. Such infusions also evoked an increase in carotid body chemoreceptor discharge.

9. It is concluded that the hyperpnoea produced by adrenaline and

noradrenaline infusions in the cat is predominantly reflex in origin and is mediated by the arterial chemoreceptors.

10. The increase in ventilation produced by adrenaline appears to have a component additional to its effect upon the chemoreceptors though the nature of this action has not been identified.

INTRODUCTION

The action of catecholamines on respiration was first examined by Oliver & Schafer (1895), who found that intravenous injections of extracts of the suprarenal capsule depressed respiration in dogs and rabbits. Their results were confirmed by many other workers, notably Langley (1901), who reported that such injections might cause complete cessation of breathing. Nice, Rock & Courtright (1914) criticized these early observations on the grounds that the doses of catecholamine had been unnaturally large, and showed that smaller doses could lead to an increase in the depth of respiration in anaesthetized cats and dogs. Young (1957) also reported hyperpnoea in response to the intravenous injection of adrenaline in the anaesthetized cat but found inhibition of respiration in the decerebrate cat. In her experiments noradrenaline depressed respiration both in the anaesthetized and in the decerebrate cat.

Intravenous infusions of small doses of adrenaline and noradrenaline have been shown to stimulate respiration in man by Whelan & Young (1953). This effect has been confirmed by, among others, Cunningham, Hey & Lloyd (1958).

The apnoea produced in animals by larger doses of adrenaline was subsequently shown by Wright (1930) to be reflex in origin, dependent on afferent impulses in the vagus and carotid sinus nerves initiated from baroreceptor endings stimulated by the concomitant rise in arterial pressure. The mechanism whereby small doses of catecholamines lead to an increase in respiratory minute volume is less well defined. Nice *et al.* (1914) suggested that it was a central effect. Others (Tompkins, Sturgis & Wearn, 1919; Boothby & Sandiford, 1923) have suggested that it is related to an effect of adrenaline on metabolism. More recently, Lee, Mayou & Torrance (1964) reported that adrenaline and noradrenaline increased the discharge of the aortic chemoreceptors at any given level of arterial pressure and they felt that this increased sensitivity of the chemoreceptors might be important for the stimulation of respiration.

The present experiments re-examine the effects of intravenous infusions of small doses of adrenaline and noradrenaline on the respiration of both anaesthetized and decerebrate animals; the contribution of the carotid and aortic reflexogenic areas to these responses has been investigated by

comparing the effects of catecholamines before and after cutting the carotid sinus and aortic nerves, and by the simultaneous recording of chemoreceptor action potential discharge and respiratory minute volume.

The response to infusion of catecholamines into one carotid artery has also been investigated in the anaesthetized cat, and the contribution of the carotid reflexogenic area to the response similarly examined by cutting the corresponding carotid sinus nerve and by recording the chemoreceptor discharge.

A preliminary account of some of this work has been given by Joels & White (1967).

METHODS

The experiments were carried out on cats, anaesthesia being induced by ethyl chloride B.P. (Ethyl chloride—Hedley) and halothane B.P. (Fluothane—Imperial Chemical Industries), and maintained by intravenous injection of 5–6 ml./kg of a 1% solution of chloralose in sodium chloride 0·9 g/100 ml. (α chloralose, Etablissements Kuhlmann, Paris, 50–60 mg/kg). In decerebration experiments cats were anaesthetized with halothane and after craniotomy the cerebrum and upper brain stem down to the mid-collicular level were removed by suction. The animals were then left for 1 hr to allow the anaesthetic to wear off before any measurements of respiration were made.

A polythene cannula was introduced into one femoral artery to permit recording of arterial blood pressure which was registered on smoked paper by a mercury manometer. In some experiments the opposite femoral artery was also cannulated; a large bore polythene cannula leading to a simple blood-pressure compensator consisting of an inverted conical flask part filled with blood. The air space above the blood was connected to a reservoir of compressed air which could be adjusted to any desired pressure. The compensator was used to minimize changes in blood pressure produced by catecholamines and in particular to ensure that in the denervation experiments the level of arterial pressure was not affected by cutting the carotid sinus and aortic nerves.

The trachea was cannulated and connected via low-resistance Perspex valves to a modification of the Donald & Christie (1949) bag-in-box spirometer described by Bacon, Daly & Scott (1962). This allowed continuous quantitative recording of respiratory rate and tidal volume both while air and various test gas mixtures were being breathed.

Intravenous infusions of adrenaline (Adrenaline tartrate B.P.—Samoore, Ltd.) and noradrenaline (Noradrenaline bitartrate, 'Levophed'—Bayer Products, Ltd.) were administered through a polythene cannula in a femoral vein. The drugs were made up in NaCl (0·9 g/100 ml.) to a concentration of 2 μg/ml., the solutions being infused at rates varying between 0·25 and 1·0 ml./kg.min (0·5 and 2·0 μg/kg.min). The dose of catecholamine used in any individual experiment was the minimum required to produce a recognizable respiratory response in that particular cat. The infusion solutions also contained ascorbic acid (0·001 g/100 ml.) to minimize the oxidation of catecholamines (Gaddum, Peart & Vogt, 1949).

Intra-carotid infusions were made through a polythene cannula introduced into a lingual artery and passed in a retrograde direction down the external carotid artery until the tip lay close to the carotid sinus. The external carotid artery was ligated immediately rostral to the origin of the lingual artery to direct a greater fraction of the infused drug through the vascular channels of the carotid body. The solution of adrenaline used for these infusions contained 1 μg/ml. and that of noradrenaline 0·5 μg/ml. These solutions were infused at a rate of 0·5 ml./min, corresponding to about 0·2 μg/kg.min adrenaline and 0·1 μg/kg.min noradrenaline.

Measurement of respiratory responses to intravenous catecholamine infusion

Animals breathing air. After completion of the necessary operative procedures the animals breathed room air through the respiratory valves until respiration was steady. Intravenous infusion of adrenaline or noradrenaline was then commenced. Though quite marked changes in blood pressure sometimes occurred in the first 1–2 min, by the 5th min of infusion the blood pressure was generally within 5 mm Hg of its value during the control period and the respiration had attained a new steady level. The effects of catecholamines in this group of animals were therefore assessed by comparing the ventilation during the 5th min of infusion with that during the last minute of the control period.

Animals breathing 100 % O_2. The procedure was identical with that described above except that 100 % O_2 was inspired throughout both the control period and the period of infusion.

Animals breathing hypoxic gas mixtures. The cat breathed room air and when the respiratory rate and depth were steady, the inspired gas was changed to 10 % O_2 in N_2 for 3 min. The animal then breathed room air until the respiration was once more steady whereupon the intravenous infusion of catecholamine was begun. After 5 min of infusion, when the blood pressure was close to its control level, the cat again inspired 10 % O_2 for a further 3 min throughout which the catecholamine infusion was continued. This experimental procedure, which was adopted to minimize the periods for which animals were subjected to a comparatively severe degree of hypoxia, is illustrated diagrammatically in Fig. 1.

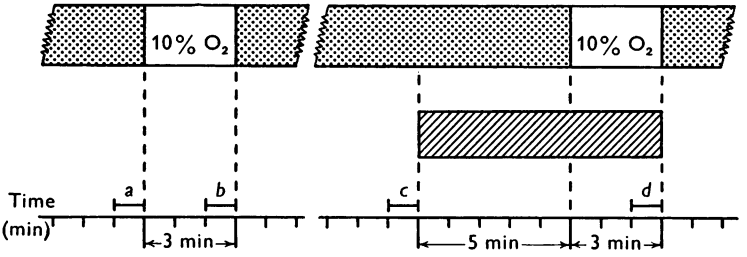

Fig. 1. Diagrammatic representation of experimental procedure used to test the effect of catecholamines on the ventilatory response to hypoxia. Room air inspired during periods indicated by stippled bars. 10 % O_2 inhaled during unshaded periods. Duration of intravenous infusion of catecholamine indicated by hatched bar. Ventilation measured during periods *a*, *b*, *c* and *d*.

The response to hypoxia alone was assessed by comparing the ventilation during the 3rd min of inhalation of 10 % O_2 (period *b*) with that during the last minute of the preceding control period (period *a*). The response to the combination of hypoxia and the intravenous infusion of catecholamine was similarly assessed by comparing the ventilation during the 3rd min of combined hypoxia and catecholamine infusion (period *d*) with that during the last minute of the preceding control period (period *c*).

In some experiments the hypoxic gas mixture was 5 % O_2 in N_2. The procedure was then similar to that used when 10 % O_2 was breathed except that the hypoxic mixture was inhaled for 2 min only. The ventilatory responses were therefore measured over the 2nd min of these periods.

Though the respiration did not attain a steady state during the inhalation of the low oxygen mixtures, strict adherence to the time intervals made the measurements with and without catecholamines comparable. Moreover, to avoid any bias due to changes in the condition of the animal during the course of an experiment, trials of the effect of hypoxia combined with adrenaline or noradrenaline infusion were always alternated with trials of the effect of hypoxia alone.

Animals breathing CO_2 mixtures. Experiments to test the effects of catecholamines on the ventilatory response to hypercapnic gas mixtures followed the same course as that described for 10 % O_2, except that 5 % CO_2 in air or 5 % CO_2 in O_2 was inhaled in place of the hypoxic mixture. When the test gas was 5 % CO_2 in O_2, 100 % O_2 was inspired instead of room air during the control periods. Measurements were similarly made over the times indicated in Fig. 1.

Statistical analysis of results. Except where specifically stated the significance of the difference between means was used to assess whether the effect of catecholamines in a particular experimental situation was statistically significant. For example, to test whether adrenaline infusion significantly increased the response to the inhalation of 10 % O_2 in N_2 the individual percentage increases in ventilation during inhalation of 10 % O_2 in N_2 were summed and the mean value determined. The mean percentage increase in ventilation when inhalation of 10 % O_2 in N_2 by the same group of animals was accompanied by adrenaline infusion was also determined. Student's t test was then applied to the data to discover whether the difference between these mean values differed significantly from zero, i.e. whether adrenaline had exerted a statistically significant effect.

Because anaesthetized cats show considerable individual variations in their responses to hypoxic and hypercapnic gas mixtures, the significance of the difference between means is probably not the most sensitive index of significance that could have been used. However, it has been selected here because it correlates with the manner in which the results are graphically presented. The effect, if any, on the findings presented in this paper will be to underestimate their statistical significance.

Chemoreceptor action potentials

To record the chemoreceptor discharge one sinus nerve was dissected out and cut centrally. Slips containing either a single active chemoreceptor fibre or a few identifiable fibres were laid on saline wick electrodes and after amplification the action potentials were displayed on one beam of a Cossor double-beam oscilloscope from which they could be photographed. The chemoreceptor origin of the fibres was always confirmed by their responses to hypoxia and carotid occlusion. Discharge frequencies were computed by counting the number of spikes in lengths of record extending over 20–30 sec.

RESULTS

Reflex responses to intravenous infusion of catecholamines

Animals breathing room air. The respiratory effects of catecholamines in anaesthetized cats breathing room air were assessed by comparing the ventilation during the last minute of the control period with that during the 5th min of the infusion. Figure 2*A* is a tracing from a typical experiment showing the respiration and blood pressure during the last minute before infusion. During the 5th min of adrenaline infusion there was an increased tidal volume and blood pressure was within 5 mm Hg of its control value (Fig. 2*B*).

The changes in ventilation during catecholamine infusion in this group of animals breathing air are summarized in Fig. 3 and Table 1. The mean increase in respiratory minute volume was 14% during the intravenous infusion of adrenaline and 8% during the intravenous infusion of noradrenaline. Both these increases were significant ($P < 0{\cdot}01$).

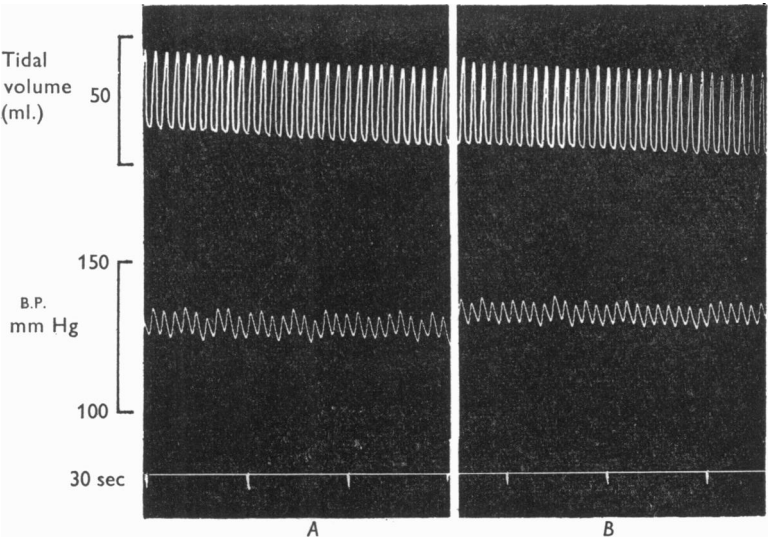

Fig. 2. Cat, 3·4 kg, chloralose anaesthesia. Effect of intravenous infusion of adrenaline on respiration and blood pressure. *A*, immediately before infusion. *B*, 5 min after commencing infusion of adrenaline 4 μg/min.

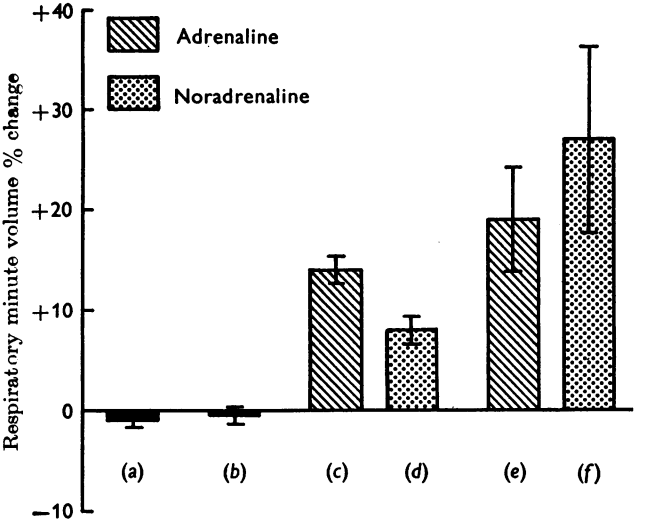

Fig. 3. Mean percentage changes in ventilation produced by intravenous infusions in cats breathing room air. (*a*) Saline. (*b*) Vehicle in which catecholamine was supplied. (*c*) Adrenaline (average dose 0·8 μg/kg.min) in anaesthetized cats. (*d*) Noradrenaline (average dose 0·8 μg/kg.min) in anaesthetized cats. (*e*) Adrenaline (average dose 1·1 μg/kg.min) in decerebrate cats. (*f*) Noradrenaline (average dose 1·4 μg/kg.min) in decerebrate cats. In this figure and Figs. 4, 5, 6, 7 and 11 the vertical lines represent $\pm$ 1 standard error of the mean (S.E.M.).

By comparison, only insignificant changes in ventilation were produced by the infusion of comparable volumes of saline (mean change −0·9%) or of an appropriate dilution of the sodium metabisulphite (0·2 g/100 ml.) in sodium chloride (0·8 g/100 ml.) vehicle in which the catecholamines were supplied (mean change −0·4%).

Decerebrate cats. The effects of adrenaline and noradrenaline were also examined in decerebrate cats breathing room air. Young (1957) found that catecholamines depressed respiration in the decerebrate cat but in the present experiments respiration was invariably stimulated by infusion of

TABLE 1. The effects of intravenous infusions of adrenaline and noradrenaline on the respiratory minute volume (R.M.V.) of anaesthetized and decerebrate cats breathing air and of anaesthetized cats breathing 100% O_2

Nature of intravenous infusion	Inspired gas	Number of cats	Number of trials	Average dose of catecholamine (μg/kg.min)	Mean change in R.M.V. ± S.E.M.	Significance of change in R.M.V.
Saline	Air	8	19	—	−0·9 ± 0·6%	$P > 0·1$
Vehicle (0·2% metabisulphite)	Air	4	12	—	−0·4 ± 0·8%	$P > 0·6$
Adrenaline, anaesthetized	Air	20	65	0·8	14 ± 1·4%	$P < 0·01$
Noradrenaline, anaesthetized	Air	11	24	0·8	8 ± 1·3%	$P < 0·01$
Adrenaline, decerebrate	Air	5	10	1·1	19 ± 5·1%	$P < 0·01$
Noradrenaline, decerebrate	Air	3	6	1·4	27 ± 9·3%	$P < 0·05$
Adrenaline, anaesthetized	100% O_2	6	22	0·8	−1·3 ± 1·0%	$P > 0·2$
Noradrenaline, anaesthetized	100% O_2	6	15	1·1	1·3 ± 1·0%	$P > 0·2$

adrenaline or noradrenaline (Fig. 3 and Table 1). The mean increase in respiratory minute volume produced by adrenaline was 19% and that by noradrenaline was 27%. Both these increases are significant: for the adrenaline infusions $P < 0·01$; for the noradrenaline infusions $P < 0·05$. No comparison has been made of the relative potencies of adrenaline and noradrenaline in the anaesthetized and decerebrate groups of animals because the number of trials in decerebrate cats was small and a wider range of doses was infused.

Since catecholamines increased the ventilation in decerebrate cats as well as in cats anaesthetized with chloralose it was concluded that chloralose anaesthesia did not qualitatively influence the responses and therefore all the subsequent experiments were performed on anaesthetized animals.

Animals breathing 100% O_2. In Fig. 4 the changes in ventilation produced by adrenaline and noradrenaline in animals breathing room air are compared with the changes produced by these drugs in animals breathing 100% O_2.

In the group of cats breathing room air the minute volume was increased 14% by adrenaline and 8% by noradrenaline, both these increases being significant ($P < 0{\cdot}01$). By contrast, when the inspired gas was 100% O_2, the mean changes during infusion of adrenaline ($-1{\cdot}3$%) or noradrenaline ($+1{\cdot}3$%) were without statistical significance ($P > 0{\cdot}2$). Fuller details of these experiments are given in Table 1.

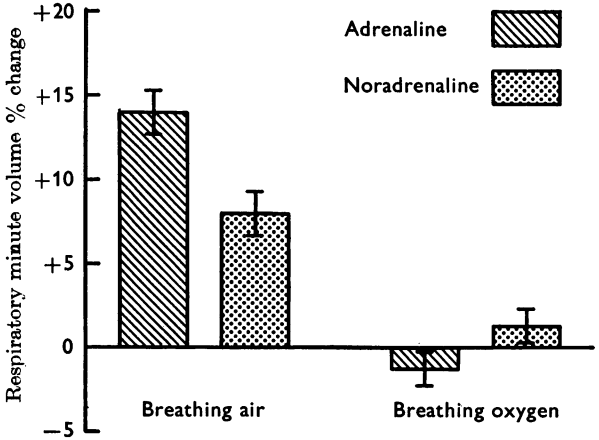

Fig. 4. Comparison of the effects of catecholamine infusion on the ventilation of cats breathing room air and 100% oxygen. During air breathing the average dose of both adrenaline and noradrenaline was 0·8 μg/kg.min. While breathing 100% oxygen the average dose of adrenaline was 0·8 μg/kg.min; that of noradrenaline was 1·1 μg/kg.min.

Animals breathing hypoxic gas mixtures. Figure 5 illustrates the effects of adrenaline and of noradrenaline on the respiration of animals breathing room air, 10% O_2 in N_2 and 5% O_2 in N_2 (see also Table 2). In these experiments with hypoxic mixtures, ventilation was measured during the periods indicated in Fig. 1. The columns represent the percentage increases in ventilation during (*a*) the 5th min of catecholamine infusion when inspiring room air; (*b*) the 3rd min of inhalation of 10% O_2; (*c*) the 3rd min of inhalation of 10% O_2 combined with the infusion of catecholamine; (*d*) the 2nd min of inhalation of 5% O_2; and (*e*) the 2nd min of inhalation of 5% O_2 combined with catecholamine infusion.

In the experiments in which adrenaline was infused (Fig. 5*A*) the mean increase in respiration during the inhalation of 10% O_2 in N_2 was 81% whereas the mean increase in respiration when the inhalation of 10% O_2 in N_2 was combined with the infusion of adrenaline was 129%. Similarly, the inhalation of 5% O_2 in N_2 produced a mean increase of 95% and the inhalation of 5% O_2 in N_2 combined with the infusion of adrenaline increased the respiration by 117%. The increases in respiration when

adrenaline infusion accompanied the inhalation of each of the hypoxic gas mixtures are significantly greater than the increases due to inhalation of 10% or 5% O_2 in N_2 alone ($P < 0{\cdot}01$).

Figure 5*B* presents the corresponding data for the infusion of noradrenaline. The mean increase in respiration during the inhalation of 10% O_2 in N_2 in this series was 70%, whereas the mean increase in respiration when the inhalation of 10% O_2 in N_2 was combined with the infusion of noradrenaline was 102%. The inhalation of 5% O_2 in N_2 produced a mean

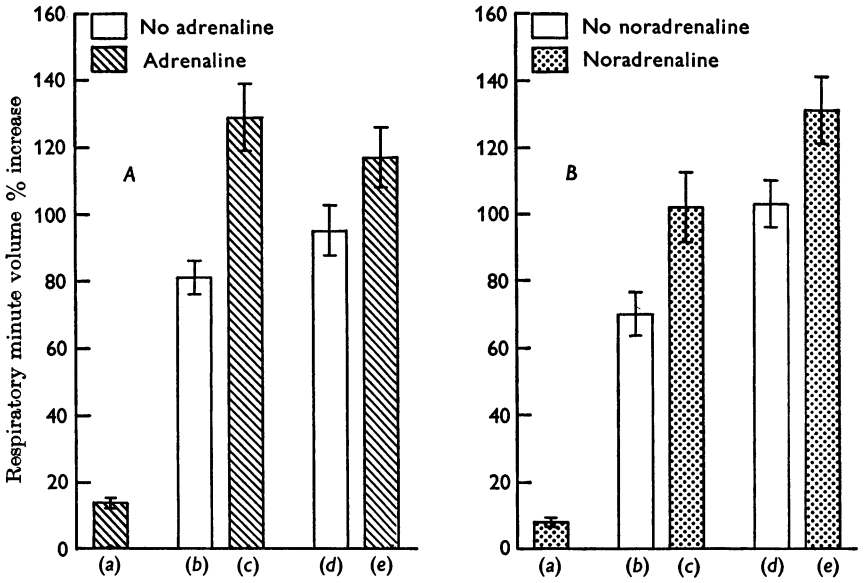

Fig. 5. Effects of intravenous infusion of catecholamines on the respiratory response to the inhalation of low oxygen mixtures.

A, experiments with adrenaline infusion. (*a*) Breathing room air and receiving adrenaline (average dose 0·8 μg/kg.min). (*b*) Breathing 10% O_2 in N_2 alone. (*c*) Breathing 10% O_2 in N_2 and receiving adrenaline (average dose 0·7 μg/kg.min). (*d*) Breathing 5% O_2 in N_2 alone. (*e*) Breathing 5% O_2 in N_2 and receiving adrenaline (average dose 0·8 μg/kg.min).

B, experiments with noradrenaline infusion. (*a*) Breathing room air and receiving noradrenaline (average dose 0·8 μg/kg.min). (*b*) Breathing 10% O_2 in N_2 alone. (*c*) Breathing 10% O_2 in N_2 and receiving noradrenaline (average dose 0·6 μg/kg.min). (*d*) Breathing 5% O_2 in N_2 alone. (*e*) Breathing 5% O_2 in N_2 and receiving noradrenaline (average dose 1·2 μg/kg.min).

increase of 103% and the inhalation of 5% O_2 in N_2 combined with the infusion of noradrenaline increased the respiration by 131%. The increases in respiration when noradrenaline infusion accompanied the inhalation of each of the hypoxic mixtures are also significantly greater than the increases due to hypoxia alone ($P < 0{\cdot}01$).

TABLE 2. The effects of intravenous infusions of adrenaline and noradrenaline on the increase in respiratory minute volume (R.M.V.) during the inhalation of hypoxic gas mixtures by anaesthetized cats

Inspired gas	Catecholamine infused	Average dose (μg/kg.min)	Number of cats	Number of trials	Mean increase in R.M.V. $\pm$ S.E.M.	Significance of catecholamine effect
10% O_2 in N_2	—	—	5	19	81 $\pm$ 4·9%	$P < 0·01$
10% O_2 in N_2	Adrenaline	0·7		13	129 $\pm$ 10·3%	
5% O_2 in N_2	—	—	6	25	95 $\pm$ 7·4%	$P < 0·01$
5% O_2 in N_2	Adrenaline	0·8		19	117 $\pm$ 8·8%	
10% O_2 in N_2	—	—	5	17	70 $\pm$ 6·1%	$P < 0·01$
10% O_2 in N_2	Noradrenaline	0·6		12	102 $\pm$ 10·4%	
5% O_2 in N_2	—	—	5	20	103 $\pm$ 6·9%	$P < 0·01$
5% O_2 in N_2	Noradrenaline	1·3		15	131 $\pm$ 10·0%	

TABLE 3. The effects of intravenous infusions of adrenaline and noradrenaline on the increase in respiratory minute volume (R.M.V.) during the inhalation of hypercapnic gas mixtures by anaesthetized cats

Inspired gas	Catecholamine infused	Average dose (μg/kg.min)	Number of cats	Number of trials	Mean increase in R.M.V. $\pm$ S.E.M.	Significance of difference between means	Mean difference $\pm$ S.E.M.	Significance of mean difference
5% CO_2 in air	—	—	4	17	61 $\pm$ 6·0%	$P > 0·2$	9·9 $\pm$ 3·4%	$P < 0·02$
5% CO_2 in air	Adrenaline	0·8		13	72 $\pm$ 6·4%			
5% CO_2 in O_2	—	—	5	23	77 $\pm$ 8·7%	$P > 0·6$	−2·2 $\pm$ 2·5%	$P > 0·3$
5% CO_2 in O_2	Adrenaline	0·9		17	71 $\pm$ 8·2%			
5% CO_2 in air	—	—	4	16	72 $\pm$ 7·1%	$P > 0·2$	7·0 $\pm$ 3·1%	$P < 0·05$
5% CO_2 in air	Noradrenaline	0·8		11	83 $\pm$ 7·7%			
5% CO_2 in O_2	—	—	5	21	70 $\pm$ 6·6%	$P > 0·6$	−2·4 $\pm$ 2·1%	$P > 0·2$
5% CO_2 in O_2	Noradrenaline	1·2		14	66 $\pm$ 8·0%			

The results of these experiments show that infusions of adrenaline or noradrenaline increased the respiration of animals breathing room air or hypoxic gas mixtures. On the other hand catecholamine infusions did not significantly alter the breathing when the inspired gas was 100% O_2.

Animals breathing CO_2 mixtures. The respiratory responses to the inhalation of hypercapnic gas mixtures alone and when combined with the intravenous infusion of adrenaline are compared in Fig. 6*A*. In this group

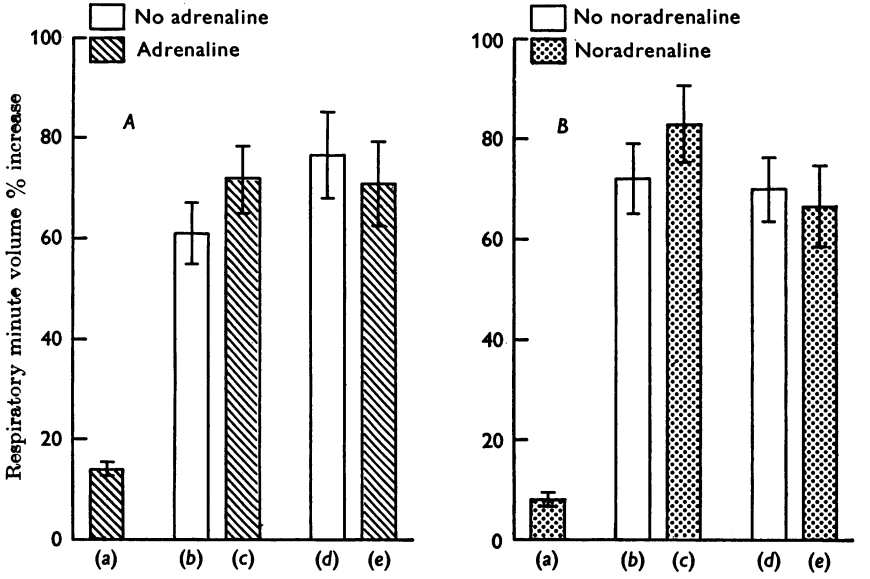

Fig. 6. Effects of intravenous infusion of catecholamines on the respiratory response to the inhalation of hypercapnic gas mixtures.

A, Experiments with adrenaline infusion. (*a*) Breathing room air and receiving adrenaline (average dose 0·8 μg/kg.min). (*b*) Breathing 5% CO_2 in air alone. (*c*) Breathing 5% CO_2 in air and receiving adrenaline (average dose 0·8 μg/kg.min). (*d*) Breathing 5% CO_2 in O_2 alone. (*e*) Breathing 5% CO_2 in O_2 and receiving adrenaline (average dose 0·9 μg/kg.min).

B, experiments with noradrenaline infusion. (*a*) Breathing room air and receiving noradrenaline (average dose 0·8 μg/kg.min). (*b*) Breathing 5% CO_2 in air alone. (*c*) Breathing 5% CO_2 in air and receiving noradrenaline (average dose 0·8 μg/kg.min). (*d*) Breathing 5% CO_2 in O_2 alone. (*e*) Breathing 5% CO_2 in O_2 and receiving noradrenaline (average dose 1·2 μg/kg.min).

of animals the inhalation of 5% CO_2 in air increased the ventilation over that in the control period when breathing air by 61%, while the inhalation of 5% CO_2 in air together with the intravenous infusion of adrenaline increased respiration by 72%. Inhalation of 5% CO_2 in O_2 increased the ventilation over that in the control period when breathing 100% O_2 by 77%; when adrenaline was simultaneously infused the increase in ventilation was 71%.

The corresponding effects of noradrenaline are shown in Fig. 6*B*. During inhalation of 5% CO_2 in air the respiration was 72% greater than that in the control period of air breathing; simultaneous infusion of noradrenaline led to an increase of 83%. When 5% CO_2 in O_2 was inspired the ventilation increased by 70% over that in the control period breathing 100% O_2 while the inhalation of 5% CO_2 in O_2 combined with noradrenaline infusion led to an increase of 66%.

The details of this series in which animals inspired hypercapnic mixtures are given in Table 3, which also shows that the mean increases in respiration when catecholamine infusion accompanied the inhalation of either 5% CO_2 in air or 5% CO_2 in O_2 did not differ significantly from the mean increases in respiration during inhalation of the hypercapnic mixtures alone. For the effects of adrenaline and noradrenaline on the responses to 5% CO_2 in air $P > 0{\cdot}2$; on the responses to 5% CO_2 in O_2 $P > 0{\cdot}6$.

The apparent absence of a significant stimulation of respiration by catecholamines in animals breathing 5% CO_2 in air is contrary to the experience of Cunningham *et al.* (1958), who found that the infusion of noradrenaline did increase the respiratory response of conscious man to hypercapnia. However, the statistic used by us was the significance of the difference of means and we are indebted to Dr Cunningham for the suggestion that because there is a wide variability in the responses of different animals to hypercapnia an alternative statistical treatment might reveal a significant effect of catecholamines in our experiments as well. Accordingly the significance of the mean difference was determined, i.e. the mean of the differences between the individual values for respiration during the combination of hypercapnia and catecholamine infusion and the average of the immediately preceding and immediately following responses to hypercapnia alone. These values are also given in Table 3 and show that during the inhalation of 5% CO_2 in air a significantly greater increase in ventilation did occur during simultaneous infusion of adrenaline ($P < 0{\cdot}02$) or noradrenaline ($P < 0{\cdot}05$). However, they confirm that catecholamines did not exert any significant effect on the response to 5% CO_2 in O_2 (adrenaline, $P > 0{\cdot}3$; noradrenaline, $P > 0{\cdot}2$).

Effects of carotid sinus and aortic nerve section. In eight cats breathing room air the effects of adrenaline and noradrenaline infusion on the ventilation were observed before and after denervation of the carotid and aortic reflexogenic areas by section of the carotid sinus and aortic nerves. The changes in systemic pressure which resulted from sectioning these nerves and from the catecholamine infusions were restricted to less than 5 mm Hg by the blood-pressure compensator. The results are illustrated in Fig. 7.

Before denervation adrenaline infusion increased the respiratory minute volume by 7% (S.E.M. $\pm 0{\cdot}9$%). Noradrenaline infusion increased

the respiration by 7·6% (S.E.M. ±0·9%). After sectioning the nerves the ventilation during catecholamine infusion was virtually identical with that during the preceding control period. Adrenaline in the same dosage as before denervation increased respiratory minute volume by an average of 0·4% (S.E.M. ±0·6%) and noradrenaline infusion, also in the same dosage as before the denervation, led to a reduction of 0·6% (S.E.M. ±0·4%). The stimulant effect of catecholamines on respiration thus appeared to be dependent on the integrity of the carotid sinus and aortic nerves.

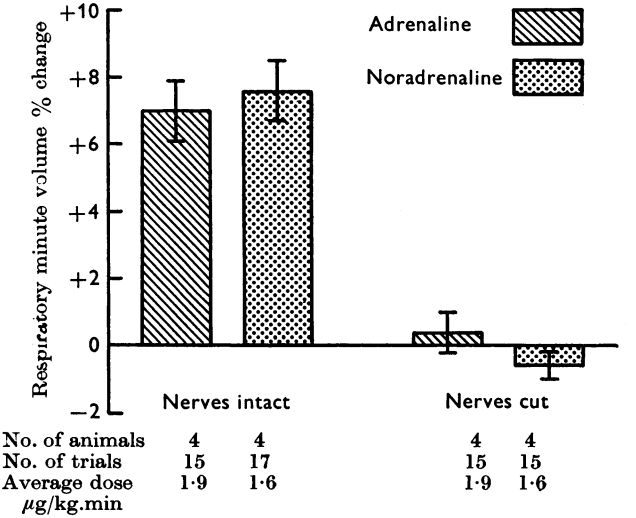

Fig. 7. Effect of carotid sinus and aortic nerve section on the respiratory response to intravenous infusion of adrenaline and noradrenaline.

Chemoreceptor discharge during intravenous catecholamine infusions

In nine cats breathing air the action potential discharge in single or few-fibre chemoreceptor preparations of the carotid sinus nerve was sampled before and during infusions of adrenaline and noradrenaline. The animals' ventilation and blood pressure were also recorded, and since only one sinus nerve was sectioned to obtain the electroneurograms, reflex effects on the breathing could still be mediated through the aortic nerves and the opposite carotid sinus nerve. Records of the discharge of a few-fibre chemoreceptor preparation in an experiment in which adrenaline was infused in a dose of 1 μg/kg.min are shown in Fig. 8.

During the infusion the discharge frequency rose from its pre-infusion level of 12·3 impulses/sec (record *a*) to 21·4 impulses/sec (record *b*), an increase of 74%; this was accompanied by an increase of 13% in the ventilation, from 270 to 305 ml./min. Five minutes after the infusion had ceased the discharge had fallen towards its pre-infusion level (record *c*).

The chemoreceptor origin of the discharge of this preparation was confirmed by the marked rise in impulse traffic when the cat was made hypoxic (record *d*).

A similar increase in chemoreceptor discharge was observed in experiments in which noradrenaline was infused, and in these animals also this was accompanied by an increase in pulmonary ventilation.

In this group of nine cats records were obtained of the discharge in twelve few-fibre chemoreceptor filaments of the carotid sinus nerve. The results of fourteen infusions (seven adrenaline, seven noradrenaline) are

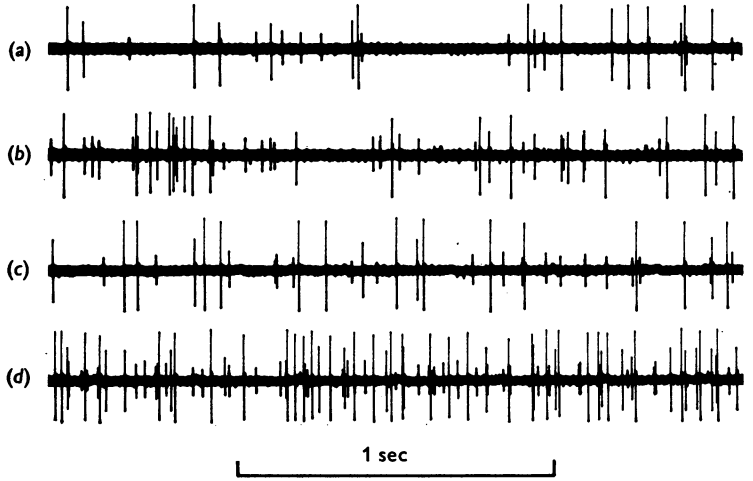

Fig. 8. Cat, 2·4 kg, chloralose anaesthesia. Effect of intravenous infusion of adrenaline (1 μg/kg.min) on discharge in a few-fibre filament of the left carotid sinus nerve. (*a*) Immediately before infusion; discharge frequency 12·3 impulses/sec, B.P. 140 mm Hg, pulmonary ventilation 270 ml./min. (*b*) 5 min after commencing infusion of adrenaline 2·5 μg/min; discharge frequency 21·4 impulses/sec, B.P. 136 mm Hg, ventilation 305 ml./min. (*c*) 5 min after ceasing infusion; discharge frequency 16·8 impulses/sec, B.P. 138 mm Hg. (*d*) Breathing 5 % O_2; discharge frequency 40 impulses/sec, B.P. 130 mm Hg.

presented in Fig. 9 in which the percentage increase in ventilation during the 5th min of the infusion is plotted against the percentage increase in the discharge frequency of the chemoreceptor fibres over the same period.

The increase in respiration produced by the infusion of catecholamines was associated in every case with an increase in chemoreceptor discharge. However, there appears to be a difference in the effects of the two catecholamines in that, with one exception, for any given increase in chemoreceptor discharge there was a tendency to a greater increase in ventilation during adrenaline infusion (filled circles) than during noradrenaline infusion (open circles).

This was especially noticeable in one of the two cats in which it was possible to record from the same fibre during infusions of both adrenaline and noradrenaline. In this experiment adrenaline infusion increased the firing frequency in the chemoreceptor filament by 11·5% with a rise of 19% in the ventilation; during noradrenaline infusion firing increased by 11% and ventilation by only 2%. In the other preparation the difference was less marked; adrenaline increased chemoreceptor firing by 66% with a rise of 8% in the ventilation while noradrenaline increased the discharge by 46% and ventilation by 4%.

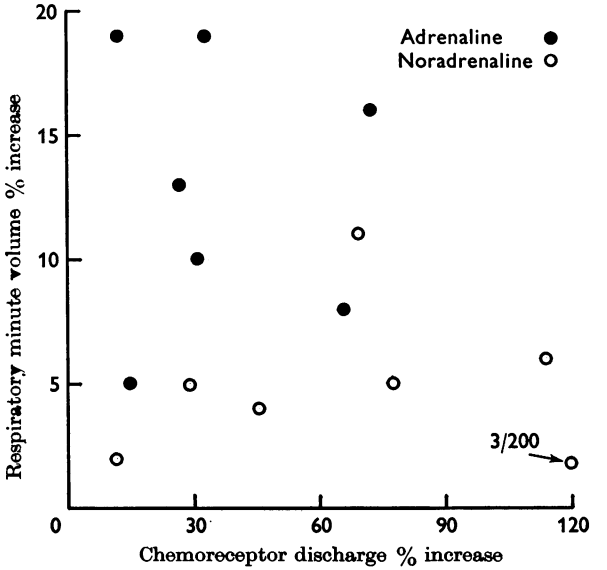

Fig. 9. Relation between the increase in ventilation and the increase in chemoreceptor discharge during infusions of catecholamines. The filled circles represent the results of adrenaline infusions; the open circles represent the results of noradrenaline infusions.

Effects of cervical sympathetic section. To determine whether the increased chemoreceptor discharge during catecholamine infusion was due to a direct effect of the drugs on the carotid bodies themselves or resulted indirectly from an alteration in the activity of the sympathetic nerves supplying them, the effects of catecholamine infusions were measured in animals in which the cervical sympathetic nerves had been divided. As it was not practicable to interrupt the sympathetic fibres supplying the aortic bodies, the influence of the chemoreceptors of the aortic region was excluded by division of both aortic nerves. As the aortic baroreceptors were denervated as well, the blood pressure was maintained within the normal limits by use of a compensator.

When the animals were infused with either adrenaline or noradrenaline there was an increase in the respiratory minute volume. Infusion of adrenaline (ten trials in four animals; average dose 1·0 μg/kg.min) increased the respiration by an average of 10% (S.E.M. ± 2·1%). Infusion of noradrenaline (nine trials in three animals; average dose 0·9 μg/kg.min) increased the ventilation by an average of 7% (S.E.M. ± 1·8%). Both these increases in respiration were significant ($P < 0·01$).

In three cats the discharge in few-fibre chemoreceptor preparations of the carotid sinus nerve was examined after division of the cervical sympathetic nerve or of the post-ganglionic branch from the superior cervical

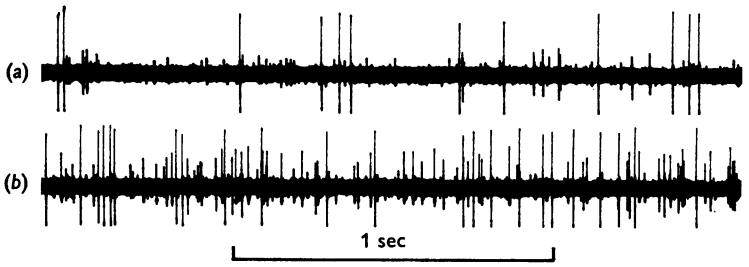

Fig. 10. Cat, 2·4 kg, chloralose anaesthesia. Effect of intravenous infusion of adrenaline on discharge in few-fibre filament of left carotid sinus nerve. Both cervical sympathetic and aortic nerves cut. (*a*) Before commencing adrenaline infusion, B.P. 126 mm Hg. (*b*) 5 min after commencing infusion of adrenaline 1 μg/kg.min, B.P. 124 mm Hg.

ganglion to the region of the carotid bifurcation. As shown in Fig. 10, which was taken from an animal after division of the cervical sympathetic nerve, infusion of adrenaline still caused an increase in chemoreceptor firing. Similar increases were obtained in the other animals during intravenous noradrenaline infusion after cervical sympathetic section.

These results demonstrate that the increase in ventilation and in carotid chemoreceptor discharge produced by catecholamine infusion is not dependent upon the integrity of the sympathetic innervation of the carotid body though they do not exclude the possibility that alterations in sympathetic discharge could contribute to these changes.

Intra-arterial infusions of catecholamines in cats breathing air

Reflex responses. The ventilatory responses to the infusion of catecholamines into one carotid artery are displayed in Fig. 11. Infusion of adrenaline increased the respiration by 9·9% (S.E.M. ± 1·1%; $P < 0·01$); noradrenaline increased ventilation by 11·5% (S.E.M. ± 2·0%; $P < 0·01$). The infusion of saline at the same rate had no significant effect on breathing (mean increase 1·7%; S.E.M. ± 1·0%; $P > 0·1$). After cutting the corresponding carotid sinus nerve respiration was unaltered by the infusion of

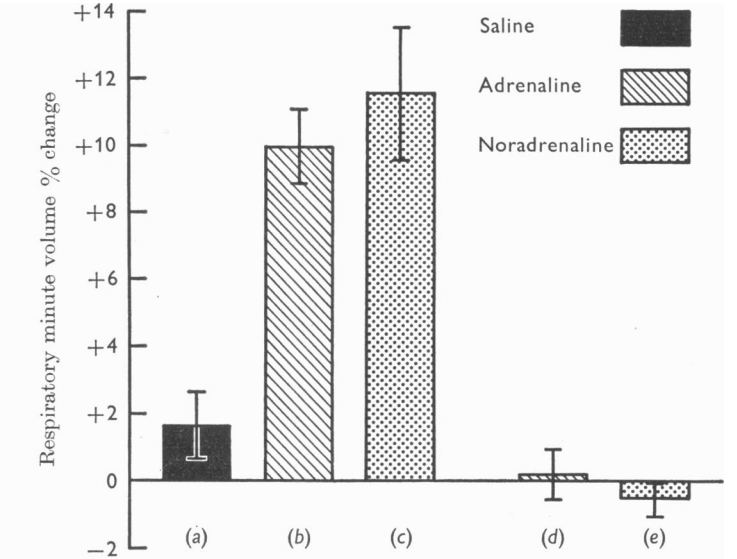

Fig. 11. Changes in ventilation produced by intra-carotid infusion of catecholamines. (*a*), (*b*) and (*c*) carotid sinus nerve intact. (*a*) Infusion of saline. (*b*) Adrenaline. (*c*) Noradrenaline. (*d*) and (*e*) After section of carotid sinus nerve on side of infusion. (*d*) Adrenaline. (*e*) Noradrenaline.

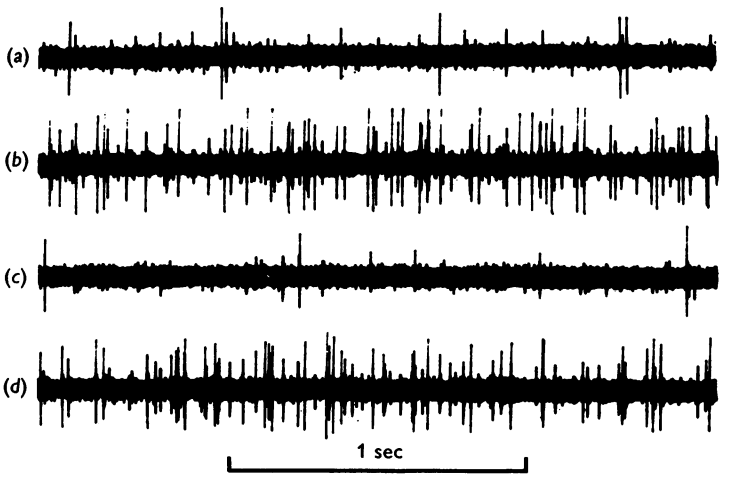

Fig. 12. Cat, 1·8 kg, chloralose anaesthesia. Effect of intra-arterial infusion of adrenaline and noradrenaline through cannula in left lingual artery on discharge in few-fibre filament of left carotid sinus nerve. (*a*) Immediately before infusion. (*b*) 2 min after commencing infusion of adrenaline 0·25 μg/kg.min. (*c*) 2 min after ceasing infusion. (*d*) 2 min after commencing infusion of noradrenaline 0·13 μg/kg.min. B.P. 120 mm Hg throughout.

catecholamines; the change in ventilation with adrenaline was +0·2% (S.E.M. ±0·7%; $P > 0·8$), with noradrenaline it was −0·5% (S.E.M. ±0·5%; $P > 0·9$).

These findings show that the local intra-arterial infusion of small doses of adrenaline and noradrenaline in the immediate vicinity of one carotid reflexogenic area stimulates the breathing and that this response is dependent on the integrity of the corresponding carotid sinus nerve. Moreover, since these small doses of catecholamines led to only minimal changes in arterial pressure it was not necessary to use a blood-pressure compensator in these experiments.

Carotid chemoreceptor discharge. Records were obtained in five cats of the discharge in filaments of the carotid sinus nerve when adrenaline and noradrenaline were infused into the corresponding carotid artery. As Fig. 12 demonstrates, the discharge increased when either of these catecholamines was infused and reverted to the control level after the infusion had been stopped.

DISCUSSION

The effects of intravenous noradrenaline infusions on the respiratory responses of unanaesthetized man have been extensively studied by Cunningham & Lloyd and their colleagues. Thus Cunningham, Hey & Lloyd (1958) found that the ventilatory response to the inhalation of mixtures of CO_2 in air was increased by the infusion of noradrenaline while Cunningham, Hey, Patrick & Lloyd (1963) showed that such infusions specifically increased the sensitivity to hypoxia, and implied that in the absence of hypoxia noradrenaline would be without effect on respiration. This conclusion was subsequently verified by Cunningham, Lloyd & Patrick (1963), who extended their observations to higher oxygen tensions.

The results of the present experiments on anaesthetized cats parallel these findings in unanaesthetized human subjects. Both adrenaline and noradrenaline infusions increased the respiration while the animals were breathing room air, low oxygen mixtures or 5% CO_2 in air, but failed to increase the respiration while the animals breathed pure oxygen or 5% CO_2 in oxygen. No attempt was made to counteract the fall in alveolar P_{CO_2} which must have taken place when the ventilation of animals breathing room air was increased by catecholamines. The work of Barcroft, Basnayake, Celander, Cobbold, Cunningham, Jukes & Young (1957) on the effect of carbon dioxide on the respiratory response to noradrenaline in man indicates that had the alveolar P_{CO_2} been held steady the effect of the infusions would have been greater. The fall in alveolar P_{CO_2} which must have accompanied hypoxic hyperpnoea would also have been still more extensive when respiration was further stimulated by the combination of

hypoxia and catecholamine infusion. The results of Cunningham, Hey, Patrick & Lloyd (1963) as illustrated by figs. 3 and 4 of their paper again suggest that had the alveolar P_{CO_2} been held steady the effect of catecholamine infusion on the response to hypoxia would similarly have been even larger.

It is arguable that our findings may have been influenced by the choice of anaesthetic since Neil, Redwood & Schweitzer (1949) demonstrated that, in cats, chloralose anaesthesia diminished the response to baroreceptor stimulation and suggested that it might also enhance the response to chemoreceptor stimulation. However, chloralose anaesthesia is unlikely to have contributed materially to the present results since anaesthetized and decerebrate cats breathing room air showed qualitatively similar responses to catecholamine infusions.

The doses of catecholamines infused intravenously (0·5–2·0 μg/kg.min), while larger than the doses (*ca.* 0·14 μg/kg.min) used by Cunningham, Hey, Patrick & Lloyd (1963), are less than the quantities of catecholamine which Celander (1954) showed could be released from the adrenal medulla of the cat during asphyxia (up to 2·5 μg/kg.min). The rates of infusion in this study can therefore be considered to lie within the physiological range.

The ability of catecholamines to increase the respiration when animals breathed room air or low oxygen mixtures, and the absence of any effect when the animals were breathing high concentrations of oxygen, suggested that their action might be exerted via the arterial chemoreceptors. This is consistent with the failure of these drugs to influence the breathing after section of the carotid sinus and aortic nerves.

Nevertheless, cutting these nerves abolishes reflex effects initiated from the baroreceptors as well as from the chemoreceptors. Catecholamines could have influenced baroreceptor discharge in the present experiments either by increasing systemic pressure or by a direct action on the wall of the carotid sinus. However, an increase in the endosinusal pressure, which increases baroreceptor discharge, leads to reflex apnoea or hypopnoea rather than hyperpnoea (Heymans, 1929). The direct action of catecholamines on the wall of the carotid sinus was investigated by Green, Heymans & Neil (1958), who applied adrenaline and noradrenaline topically in relatively high concentrations and found an increase in baroreceptor discharge. Thus a decrease in respiration rather than an increase would similarly be expected to result from the local action of catecholamines on the baroreceptors.

The hyperpnoea during intravenous catecholamine infusion when the carotid sinus and aortic nerves were intact can therefore be ascribed with some confidence to stimulation of the carotid and aortic body chemore-

ceptors. This interpretation is supported by our observation that the chemoreceptor discharge increased during the intravenous infusions.

The absence of any effect of catecholamine infusion on the respiratory response to the inhalation of 5% CO_2 in O_2 deserves some comment. Though a rise in arterial P_{CO_2} does stimulate the chemoreceptors (Euler, Liljestrand & Zotterman, 1939), at near-normal levels of P_{O_2} a rise in P_{CO_2} exerts a more powerful stimulation of respiration by a central action (Schmidt & Comroe, 1940). Furthermore, Neil & Joels (1963) have shown that in the absence of hypoxia CO_2 is a most ineffective stimulant to the arterial chemoreceptors, the discharge from the carotid body of an anaesthetized cat breathing 5% CO_2 in O_2 being little different from that when the animal breathed 100% O_2. Therefore if, as envisaged, adrenaline and noradrenaline stimulate respiration by sensitizing the chemoreceptors, it is understandable that they should have no effect during the inhalation of 5% CO_2 in O_2 when the discharge would be minimal.

Intra-carotid infusions of catecholamines. The respiratory response to intra-carotid infusions of adrenaline and noradrenaline has been examined in man under local anaesthesia by Coles, Duff, Shepherd & Whelan (1956). They found that doses of 1–2 μg/min of adrenaline or noradrenaline were without effect upon ventilation, though infusion of 10 μg/min of adrenaline did increase the ventilation in two subjects. The composition of the inspired gas was not specified in their paper, but since these were incidental observations made in patients on whom cerebral angiography was being carried out for diagnostic purposes they may have been receiving 100% O_2. This would account for the absence of respiratory stimulation by the smaller doses of catecholamines. Young (1957) similarly noted that intra-carotid injections of adrenaline and noradrenaline in cats did not alter the ventilation. However, in Young's experiments the injections were made into the common carotid artery rostral to an occluding bulldog clip and, as Lee *et al.* (1964) pointed out, under these conditions the chemoreceptors are already discharging heavily, stimulated by stagnant hypoxia. On the other hand Byck (1957) reported briefly that injections of noradrenaline into the carotid artery in anaesthetized dogs did evoke a reflex stimulation of respiration.

In our experiments the intra-carotid infusion of catecholamines also led to an increase in ventilation. The absence of an increase after the corresponding carotid sinus nerve had been cut and the increase in chemoreceptor discharge during infusion argue in favour of chemoreceptor participation in the response. This view is strongly supported by the observation that when catecholamines were placed in the immediate vicinity of one carotid body by intra-arterial infusion in doses as small as 0·1–0·2 μg/kg.min, the increase in ventilation was comparable with that produced by the intra-

venous infusion of 0·5–1·5 μg/kg.min. Though the dose of catecholamine administered by intracarotid infusion was only about one fifth of that given by intravenous infusion, one common carotid artery undoubtedly received less than one fifth of the cardiac output and, moreover, the common carotid flow on the side of the intra-arterial infusion would have been reduced by ligation of the external carotid artery. Thus the concentration of catecholamine at the corresponding carotid body would have been greater during intra-arterial infusion, as is evidenced by the greater increase in chemoreceptor discharge during the administration of adrenaline (compare Fig. 8 with Fig. 12). On the other hand intra-carotid infusion produced an effective concentration of catecholamine at one carotid body only, whereas during intravenous infusion all the peripheral chemoreceptors were exposed to an effective concentration of the drug.

Mechanism of action of catecholamines on arterial chemoreceptors. Adrenaline and noradrenaline stimulate the arterial chemoreceptors presumably through a reduction in local blood flow for, as Landgren & Neil (1951) have demonstrated, the carotid body chemoreceptors are extremely sensitive to stagnant hypoxia. This suggestion may appear inconsistent with the observations of Daly, Lambertsen & Schweitzer (1954), who, in their classic study of carotid body blood flow, found that intravenous injections of 10–25 μg adrenaline increased the flow through the carotid body. However, in these experiments of Daly *et al.* (1954) the injections of adrenaline also produced a rise in systemic pressure which must have been more than sufficient to overcome the local vasoconstrictor action at the glomus. In some unpublished experiments of their series in which a compensator was used to prevent the rise in systemic pressure, adrenaline injections did reduce carotid body blood flow (M. de B. Daly, personal communication). Neil & Joels (1963) showed that when the glomus was perfused with a constant head of pressure, the addition of noradrenaline to the perfusate led to an increased chemoreceptor discharge, again presumably through an increase in the local vascular resistance and a consequent reduction in flow. Lee *et al.* (1964) found that intravenous injection of noradrenaline led to an increased discharge in single fibres from the aortic chemoreceptors at any given level of mean arterial pressure. In our experiments on cats breathing room air in which a compensator was used to minimize changes in blood pressure, infusions of adrenaline and noradrenaline similarly increased the discharge in fibres from the carotid chemoreceptors and this increase in chemoreceptor discharge was accompanied by an increase in ventilation.

The blood vessels of the carotid body receive a rich innervation from post-ganglionic branches of the superior cervical ganglion. Floyd & Neil (1952) found that the discharge in these fibres was intensified during anoxia and haemorrhage, situations in which there is known to be an in-

crease in the firing of the chemoreceptor fibres in the carotid sinus nerve. Electrical stimulation of the post-ganglionic sympathetic fibres also increased the chemoreceptor discharge. Daly *et al.* (1954) stimulated the peripheral end of the cut cervical sympathetic while measuring carotid body blood flow and noted that this reduced the flow by as much as 55% of the control value. However, the increase in ventilation and in chemoreceptor discharge during catecholamine infusion in animals in which both cervical sympathetic and aortic nerves had been divided, shows that any increase in the discharge of the sympathetic fibres to the carotid body which might have occurred during the infusion was not essential for this response.

While all the evidence strongly suggests that the hyperpnoea of catecholamine infusion is due predominantly to a chemoreceptor reflex there remains the possibility that other mechanisms may participate in the response. Adrenaline, though not noradrenaline, may give rise to metabolic acidosis by stimulating glycolysis. On the other hand, noradrenaline can promote cerebral vasoconstriction (Sokoloff, 1959). It is also conceivable that these drugs may affect the activity of central nervous mechanisms which are depressed by anaesthesia or bodily removed by decerebration. A suggestion that adrenaline may have an action in promoting hyperpnoea in addition to that on the chemoreceptors is afforded by Fig. 9, which shows that when a given increase in chemoreceptor activity is produced by adrenaline, the increase in ventilation is greater than for a similar increase in chemoreceptor discharge produced by noradrenaline. In view of the failure of adrenaline to stimulate respiration after chemoreceptor denervation this additional effect of adrenaline might be a facilitation of the response of some central mechanism to the afferent impulses from the chemoreceptors.

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