J. Physiol. (1957) 137, 374–395

SOME OBSERVATIONS ON THE MECHANISM OF ADRENALINE HYPERPNOEA

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(*Received* 18 *March* 1957)

Although large intravenous doses of adrenaline often cause apnoea in anaesthetized animals, hyperpnoea is frequently produced (Brown, 1916; Roberts, 1921; Bouckaert, 1922; McDowall, 1928; Schmidt, 1929; Heymans & Bouckaert, 1930; Wright 1930; Hoff, Breckenridge & Cunningham, 1950). However, this stimulation of respiration is most readily observed in response to relatively small doses of adrenaline in the lightly anaesthetized animal (Nice, Rock & Courtright, 1914; Nice & Neill, 1925; Amoroso, Bell, King & Rosenberg, 1949). Moreover, a hyperpnoea is the only respiratory response seen after the injection of adrenaline in the conscious animal or in conscious man (Fuchs & Roth, 1912; Tompkins, Sturgis & Wearn, 1919; Bornstein, 1921; Lyman, Nicholls & McCann, 1923; Boothby & Sandiford, 1923; Cori & Buchwald, 1930; Courtice, Douglas & Priestley, 1939; Whelan & Young, 1953).

Adrenaline hyperpnoea is therefore a well-established effect and it is probably the physiological response of the respiratory mechanism to adrenaline. The mechanism of this hyperpnoea is still ill defined. The increased respiration is brought about chiefly by an increase in tidal volume with little alteration in respiratory rate in both the anaesthetized animal (Nice *et al.* 1914; Jackson, 1916; Nice & Neill, 1925) and in conscious man (Boothby & Sandiford, 1923; Cori & Buchwald, 1930; Courtice *et al.* 1939; Whelan & Young, 1953). In the anaesthetized animal it has been shown to be independent of changes in cerebral or systemic blood pressure and of the integrity of the vagus (Nice *et al.* 1914; Nice & Neill, 1925). It has been suggested that the hyperpnoeic response is due to the direct stimulating action of adrenaline on the respiratory centre (McDowall, 1928; Heymans & Bouckaert, 1930; Wright, 1930) or that it is simply the result of the increased metabolic rate (Boothby & Sandiford, 1923). By itself the second explanation seems scarcely sufficient, for both adrenaline and noradrenaline stimulate respiration to a comparable degree in man, in spite of the lack of any consistent increase in oxygen consumption after the

injection of noradrenaline (Whelan & Young, 1953). Finally, Courtice *et al.* (1939) attributed to lactic acid production the respiratory stimulation which they observed in man in response to adrenaline. However, both in these and in more recent experiments (Bradley, Gaskell, Holland, Lee & Young, 1954) the blood lactate peak succeeded the height of the respiratory response, indicating that the hyperpnoea is not obviously related to the blood lactate; these experiments do not, however, exclude the possibility of a raised tissue lactic acid as being the stimulus.

This investigation was therefore undertaken to throw more light on the mode of action of adrenaline in stimulating respiration in the anaesthetized cat, rabbit and dog, in the conscious rabbit and in the decerebrate cat. The effect of noradrenaline on respiration was also studied under these conditions. The possible relationship between the results obtained in these experiments with those observed in conscious man are discussed, together with the possible role of adrenaline in the respiratory response to stress.

METHODS

Most of the experiments were carried out on cats under light chloralose anaesthesia, 50 mg/kg, with the additional injection of 5–15 mg of pentobarbitone sodium (Nembutal, Abbott Laboratories) to each cat, to steady the respiratory base line. Under deep anaesthesia adrenaline hyperpnoea was not readily obtained. Rabbits, dogs and cats anaesthetized with Nembutal, 35–50 mg/kg given intravenously or intraperitoneally, were also studied, together with a few decerebrate cats and a few conscious rabbits.

Records of respiratory rate and minute volume were obtained with Paton's (1949) variable leak recorder attached to the expiratory side of a respiratory valve fitted to the tracheal cannula or to a rubber balloon which fitted on to the snout of the conscious rabbits. Arterial blood pressures were measured in the left femoral artery, with a mercury manometer.

L-Adrenaline tartrate (British Drug Houses) and noradrenaline (Levophed, Bayer Products) were made up in 0·9% NaCl solution with 0·001% ascorbic acid (Gaddum, Peart & Vogt, 1949). The drugs were always injected, whether intravenously or intra-arterially, in 0·5 ml. of the saline ascorbic acid mixture, followed by 0·5 ml. of this alone. Continuous infusions were given at the rate of 1 ml./min for 5–15 min. The preservative solutions in which the adrenaline and noradrenaline were supplied were obtained from the drug houses and suitable dilutions were injected in contro experiments.

Respiratory centre — *Site of action of amines*

To determine whether the amines were acting directly on the respiratory centre, injections were made directly into the medulla through the vertebral artery. The brachial artery was cannulated at the elbow with no. 1 polythene tubing closed with fine Spencer–Wells forceps; with the exception of the vertebral artery, all the branches of the subclavian, axillary and brachial arteries were ligated; the common carotid was clamped before a series of injections. On three occasions this preparation was carried out on both sides.

Sensory endings

To establish whether the amines were acting at sensory nerve endings and causing reflex changes of respiration the following procedures were carried out either singly or in various combinations.

The carotid and aortic afferents were investigated (i) by making injections of adrenaline directly into the carotid artery above a ligature of the common carotid on one side; (ii) by denervating the

carotid sinus region, by completely stripping the common and external carotids and tying off the small internal carotid artery, (iii) by denervating the aortic arch region and the subclavian-carotid junction, on the right side, by cutting the aortic nerves as they leave the superior laryngeal nerves (Green, 1954). The respiratory base line was frequently very irregular in these preparations.

The thoracic afferents which might be carried in the vagus nerve were studied in experiments in which both nerves were cut in the neck. Good respiratory base lines were again difficult to obtain and this procedure was most successful when the initial rate of respiration was rapid and the bilateral vagal section caused less drastic slowing of the respiratory rate.

Other afferents. Afferents in the thoracic region, and those of more caudal regions, were also investigated by complete division of the spinal cord between L2 and C8. No fall in arterial blood pressure occurred until the division was made above T5. The higher the resting B.P., and the sooner after inducing anaesthesia the division was made, the smaller the fall in pressure. In some experiments the splanchnics were cut, through a mid abdominal incision, as they emerged from the pillar of the diaphragm to relay in the solar plexus.

Skeletal muscle

To determine whether adrenaline was influencing skeletal muscle directly, maximal contractions of the gastrocnemius muscle, elicited by stimulation of the peripheral end of the sciatic nerve, were recorded simultaneously with the respiration in some experiments.

Indirect action

It appeared possible that adrenaline acted after it was converted into, or released, some other substance. To determine whether any specific organ was responsible for the 'activation' of adrenaline or the release of some other active substance, intravenous injections of adrenaline were made into a femoral vein after (1) removal of the suprarenal glands, (2) ligation of the blood supply to the kidney, and (3) removal of the entire gut; it was found difficult to remove the liver so as to preserve a good respiratory base line after the operation, so a 'head and thorax animal' was prepared as follows. The aorta and inferior vena cava were ligated in the pelvic region above their division into the iliac branches; a small catheter with an inflatable rubber balloon tied to one end (Farber & Eichna, 1953), was passed up each vessel till the balloon lay just above the passage of the vessel through the diaphragm. The exact position was checked post-mortem. Syringes were fitted to the catheters and the balloons inflated with 1·5–2 ml. of air; the inferior vena cava was occluded first, occlusion of the aorta followed immediately and was always accompanied by a rise of some 30–40 mm Hg pressure in the carotid artery.

Effect of gaseous changes

To study the effect of low oxygen tensions and high CO_2 tensions on the sensitivity of the 'adrenaline hyperpnoea' response, a Douglas bag containing the gas to be studied was attached to the inspiratory side of the respiratory valve. 10% O_2 in N_2 was breathed for 10 min and the respiratory base line was steady before the adrenaline was injected. 5% CO_2 in O_2 was used to give increased CO_2 tensions; in cats the respiratory base line was frequently unaltered by inspiring this gas, but a good stimulation was obtained in rabbits and the effect of adrenaline had to be recorded on a rising base line.

RESULTS

Intravenous injection

Adrenaline. In the intact animal hyperpnoea could be produced with injections of 0·12–0·5 μg adrenaline into a femoral vein in the average intact 2·5–3·5 kg cat, under chloralose or Nembutal anaesthesia. Out of 98 cats 37 were less sensitive and only showed a hyperpnoea with 2–5 μg adrenaline. The five types of response which could be obtained are shown in Fig. 1,

together with the accompanying arterial blood-pressure changes. A rise in the base line of the respiratory record indicates an increase in minute volume. The pure diluted preservatives in which the adrenaline and noradrenaline are supplied were without effect on respiration in the cat and the rabbit.

Fig. 1 (*a*) and (*b*) show the simple increase in minute volume caused by a small rise in tidal volume. The hyperpnoea was frequently preceded by an inhibition of respiration, as shown in Fig. 1 (*c*); this double response was more usually seen with large doses of adrenaline (Fig. 1*d*). Fig. 1*e* shows the gasp which sometimes preceded the hyperpnoea; this response was frequently seen

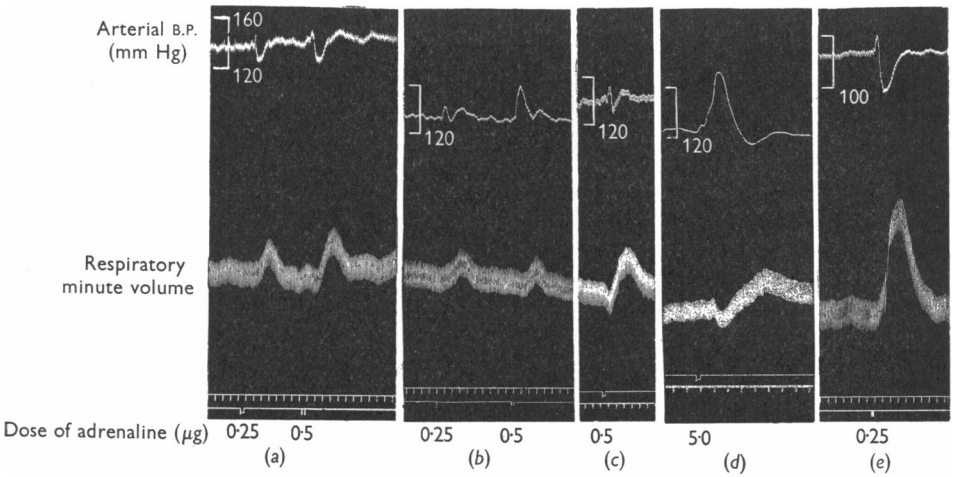

Fig. 1. The different types of respiratory response to an intravenous injection of adrenaline in the intact anaesthetized cat, together with the accompanying changes in arterial blood pressure. A rise in the base line of the respiratory record indicates an increase in minute volume. In Figs. 1–8 time marker = 10 sec.

with the first few injections of adrenaline in the experimental animal; it wore off and was replaced by a simple hyperpnoea. Continuous infusions at the rate of 1–2 μg/min caused a hyperpnoea which was permanent or which lasted for the duration of the infusion. Four decerebrate cats were studied and a marked respiratory depression always observed (Fig. 2). A stimulation of respiration was observed in anaesthetized dogs. This was preceded by an inhibition both in the intact and deafferented animals. Hyperpnoea was observed in the anaesthetized and in the conscious rabbit.

The respiratory responses to intravenous injections of adrenaline were usually accompanied by a small, short-lasting rise of arterial pressure followed by a fall of 10–20 mm Hg (Fig. 1*a*). Fig. 1*b* shows that with these doses there was sometimes a simple rise in arterial pressure accompanying the stimulation of respiration. With bigger doses of adrenaline (Fig. 1*d*) there was always a rise in blood pressure in the cat.

Most of the results to be described subsequently are concerned with the two responses most frequently observed. The first was the simple stimulation of respiration in response to very small doses of adrenaline, which was observed most frequently in a newly anaesthetized animal and was usually accompanied by a small fall in blood pressure. The second was a stimulation, preceded by a short period of inhibition of respiration, obtained with larger doses of adrenaline during the latter part of an experiment, and accompanied by a rise in blood pressure. The negative or positive effect of any experimental procedure upon the respiratory response to adrenaline or noradrenaline was accepted if the same result was obtained in at least 3–5 experiments.

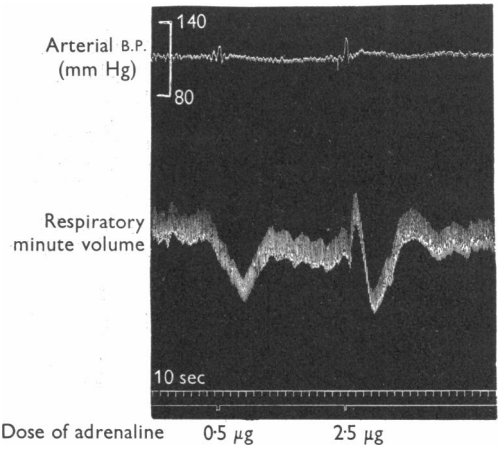

Fig. 2. The respiratory response to intravenous adrenaline in the decerebrate cat; otherwise the animal was intact.

Noradrenaline. In the anaesthetized cat and dog a small inhibition of respiration was always observed with doses of noradrenaline equivalent to those which produced hyperpnoea with adrenaline (Fig. 3*a*); small doses of noradrenaline also inhibit respiration in the decerebrate cat. But in the anaesthetized and the conscious rabbit a stimulation of respiration was always produced (Fig. 3*b*, *c*). The intravenous injections of noradrenaline were accompanied by a rise of blood pressure (Fig. 3*a*) which might be succeeded by a small fall (Fig. 3*b*).

Intra-arterial injection

To study the direct action of adrenaline and noradrenaline on the respiratory centres, injections were made into the vertebral artery of the anaesthetized cat and rabbit. 0·12–0·25 μg adrenaline either had no effect on respiration or caused an increase in minute volume which was smaller than that produced by the same dose given intravenously (Fig. 4*a*, *b*). Larger doses, up to 5 μg adrenaline, were without further direct central action, and smaller injections,

down to 0·002 μg were without effect. Similarly, intra-arterial injections of noradrenaline had no effect on breathing or an inhibitory action which was smaller than that produced by the same dose given intravenously.

The blood-pressure changes accompanying the intra-arterial injections of adrenaline were always small; the pressure rose and never fell (Fig. 4*a*). Similarly, smaller rises in blood pressure were obtained with intra-arterial noradrenaline than with equivalent doses given intravenously.

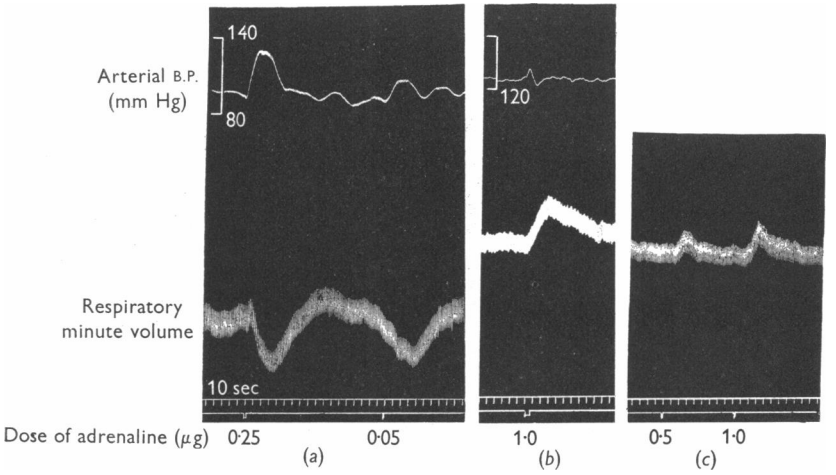

Fig. 3. The respiratory response to intravenous noradrenaline in the intact (*a*) anaesthetized cat; (*b*) anaesthetized rabbit; (*c*) conscious rabbit.

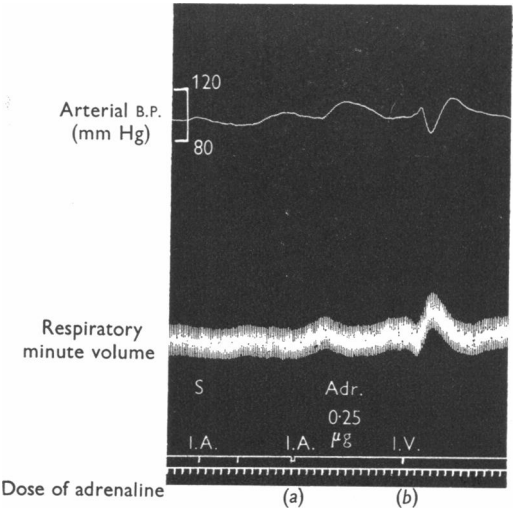

Fig. 4. A comparison between the effect of equivalent doses of adrenaline injected either into the vertebral artery (*a*) or femoral vein (*b*) in the intact anaesthetized cat.

Sensory nerve endings

To establish whether the amines were acting at sensory nerve endings and causing reflex changes of respiration, the respiratory response to the amines was not abolished by denervation of the carotid and aortic buffer regions either before or after vagal section (Fig. 5*b*) in the cat, dog and rabbit. These procedures frequently decreased the sensitivity of the preparation permanently, and response could usually only be obtained with larger doses. Injection of adrenaline or noradrenaline directly into the common carotid towards the head (above a 'bulldog' clip) produced no respiratory response.

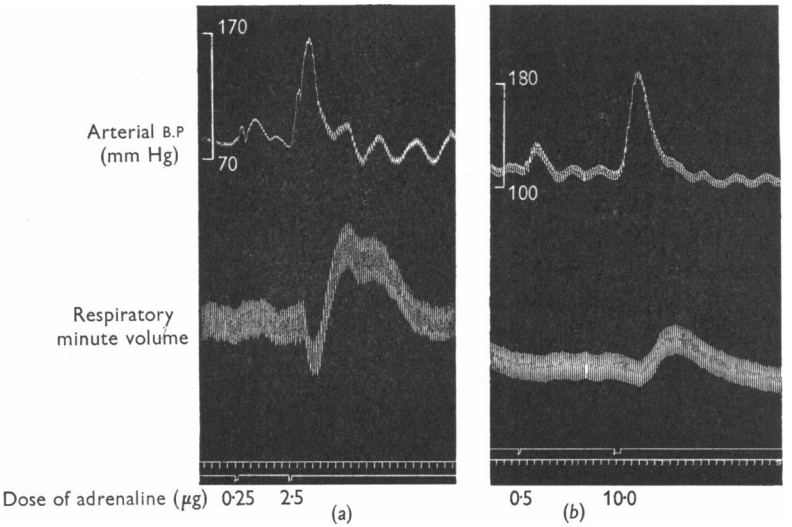

Fig. 5. The respiratory response of the anaesthetized cat to intravenous adrenaline (*a*) after dividing the vagi; (*b*) after dividing the vagi and denervation of the carotid and aortic buffer regions.

Adrenaline hyperpnoea was not abolished by section of the vagi in the cat (Fig. 15*a*), the dog or the rabbit; in the experiments in which there was a very marked slowing of respiration after division of both vagi, the response to adrenaline was temporarily abolished, but returned as the respiration rate accelerated. Similarly, the response to noradrenaline was unaltered by dividing the vagi.

Adrenaline hyperpnoea and the diminished respiration in response to noradrenaline in the cat, were not abolished by section of the cord, but when the cord was divided at T5 or above the sensitivity of the preparation was greatly decreased; a similar loss of sensitivity occurred when the splanchnic nerves were cut in the abdomen.

In the cat, after denervation of the carotid and aortic buffer regions, cutting the vagi or transection of the cord, the doses of adrenaline required to produce a response usually caused a rise in blood pressure (Fig. 5*a*, *b*).

Skeletal muscle

Fig. 6 shows that the tension developed in the gastrocnemius muscle, on stimulation of the sciatic nerve, is unaltered by both small and large doses of adrenaline, which cause a marked stimulation of respiration.

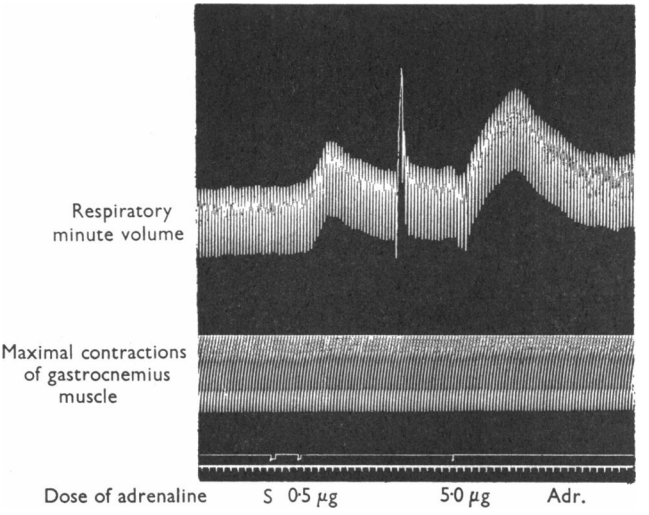

Fig. 6. A simultaneous recording of (1) maximal contractions of the gastrocnemius muscle, elicited by stimulation of the peripheral end of the sciatic nerve; and (2) respiratory minute volume, in the cat in response to adrenaline given intravenously.

Indirect action

To determine whether adrenaline acted after it was converted into or released some other substance the following experiments were performed. In the cat, removal of the suprarenal glands, the kidneys or the alimentary canal did not influence the respiratory response to intravenous injections of adrenaline; the operative procedures reduced the sensitivity of the preparation. Removal of the liver from the circulation, in the 'head and thorax' preparation, likewise did not influence the response.

Effect of gaseous changes

Low oxygen tensions in the arterial blood reduced the sensitivity of both cats and rabbits to the stimulating action of adrenaline on respiration; the breathing of mixtures containing high CO_2 tensions did not alter the sensitivity in either animal. The decrease in sensitivity in the cat due to low O_2 tensions

was irreversible, but in the rabbit it was readily reversible as seen in Fig. 7. The breathing of a high O_2 tension decreased the sensitivity of the rabbit to adrenaline, but in the cat it had either no influence or a small stimulating action.

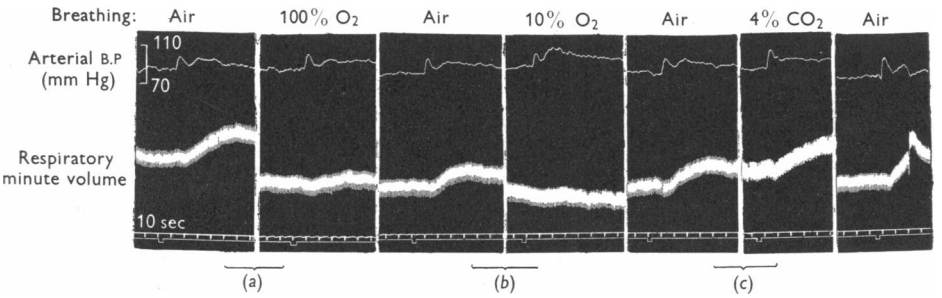

Fig. 7. The influence of (*a*) increasing the O_2 tension; (*b*) decreasing the O_2 tension; and (*c*) increasing the CO_2 tension in the inspired air, on the respiratory response to intravenous adrenaline in the anaesthetized rabbit. 2·5 μg adrenaline at each signal.

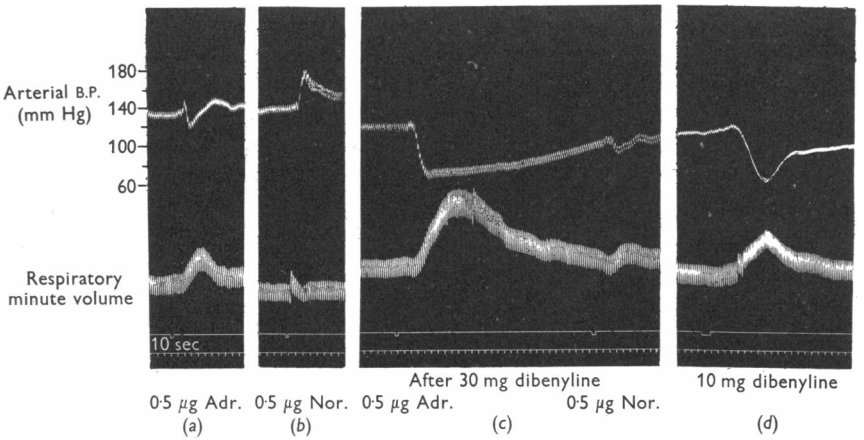

Fig. 8. To demonstrate that dibenyline does not antagonize the respiratory responses to adrenaline and to noradrenaline given intravenously in the intact anaesthetized cat (Nembutal). (*a*) and (*b*) are the control responses; and (*c*) shows that, in this experiment, dibenyline enhances the respiratory response to adrenaline; (*d*) shows that an intravenous injection of dibenyline stimulates respiration and lowers the arterial B.P. temporarily.

Influence of dibenyline

Dibenyline, given intravenously in doses up to 4 mg/kg, was without influence on the respiratory response to either adrenaline or noradrenaline given intravenously in the intact cat. Fig. 8 shows that, after a dose of 10 mg/kg of dibenyline, the respiratory response to adrenaline was greatly enhanced and the response to noradrenaline a little prolonged; this was the

only preparation in which a slight stimulation of respiration was ever seen with noradrenaline. It will be observed that the blood-pressure response to adrenaline lost its biphasic character after dibenyline and that the response to noradrenaline was reversed so that there was a fall in arterial blood pressure after the injection of either of the amines.

Fig. 8*d* shows that dibenyline itself caused a stimulation of respiratory rate and an increase in minute volume; the arterial blood pressure was temporarily depressed.

DISCUSSION

Adrenaline hyperpnoea was readily observed in the intact cat, dog and rabbit lightly anaesthetized with chloralose or Nembutal, after single injections of small doses 0·05–0·25 μg/kg. The increase in minute volume was achieved by an increase in tidal volume with only a minimal increase in rate, as observed by Nice *et al.* (1914), Nice & Neill (1925), Jackson (1916) and McDowall (1928); Garrelon & Langlois (1913) found a marked acceleration of respiratory rate in dogs. The type of response varied with each preparation and the duration of the anaesthesia.

The first response, a sigh, was observed in one-third of the preparations studied. Its abruptness suggests the direct stimulation by adrenaline of a central or peripheral mechanism and resembles the abrupt onset of hyperpnoea seen in man (Whelan & Young, 1953).

The second response, the simple increase in minute volume, most frequently observed with the small doses of adrenaline in the newly anaesthetized animal which had undergone no extensive dissection, was accompanied by either a small fall in the arterial blood pressure or a small rise. This response is therefore independent of changes in the arterial pressure, as observed by Nice and his colleagues.

The third response, an increase in the minute volume, which was preceded by a short period of inhibition of respiration, was obtained with the large doses of adrenaline (0·5–2·0 μg/kg) which were always required to elicit the response 1 hr after induction of anaesthesia or after extensive dissection. The small inhibition of respiration corresponded in time with the beginning of the rise in arterial blood pressure of some 40 mm Hg which accompanied these injections: it was, however, not the reflex adrenaline apnoea seen by Heymans & Bouckaert (1950) and by Wright (1930), for it always persisted after section of the vagi, denervation of the carotid sinus mechanisms and section of the cord at the level of C8; furthermore, the hyperpnoea in this third type of response was well established before the blood pressure fell to control values again.

The sustained hyperpnoea in response to a continuous infusion of adrenaline in the anaesthetized animal resembled the response of conscious man, breathing high CO_2 tensions, to a continuous infusion of adrenaline or noradrenaline

(Barcroft, Basnayake, Celander, Cobbold, Cunningham, Jukes & Young, 1956); one reason for this similarity might have been the accumulation of CO_2 in the anaesthetized animal due to the depression of respiration by the anaesthetic, but no results were obtained to define the extent to which the latter had occurred.

The inhibition of respiration by noradrenaline in the anaesthetized animal was of particular interest because a species difference was found; in the cat and dog an inhibition was observed, in contrast with the stimulation observed in the rabbit and conscious man (Reale, Kappert, Skoglund & Sutton, 1950; Whelan & Young, 1953). It is not known whether the response in the cat and dog was reversed by anaesthesia, but in the rabbit a stimulation was observed both with and without an anaesthetic. It is striking, too, that both adrenaline and noradrenaline inhibited respiration in the decerebrate cat.

Reflex stimulation of respiration by adrenaline

These responses to adrenaline and noradrenaline, just described, are independent of the integrity of the vagus, the cervical sympathetic, the carotid sinus and aortic arch mechanisms and the cord below the level of C8. That adrenaline and noradrenaline should cause hyperpnoea in man by causing vasoconstriction in the carotid and aortic body regions, with the development of a local decrease in oxygen tension and a high CO_2 tension, had seemed an attractive hypothesis. However, the experimental evidence in animals renders this explanation unlikely because (1) no responses followed the direct injection of the amines into the common carotid artery towards the bifurcation, (2) the responses observed after intravenous injections persisted after denervation of both carotid and aortic body regions, and (3) adrenaline hyperpnoea was not abolished by the adrenergic blocking agent, dibenyline, in confirmation of previous work on adrenergic blocking agents (Nickerson & Goodman, 1947). Lastly, Daly, Lambertsen & Schweitzer (1954) found that doses of 10–25 μg adrenaline in the cat increased the carotid body blood flow 12–43%, and a further increase to 67% was obtained with 100 μg adrenaline; these increases in flow were due to the rise in arterial blood pressure. Palme (1936) and Landgren, Neil & Zotterman (1952) applied 1:1,000 adrenaline to the surface of the carotid sinus region and observed a constriction of the vessel walls, increased activity in the carotid sinus nerve and a reflex fall in arterial blood pressure. No hyperpnoea was observed (Neil, personal communication).

In the absence of positive evidence for the involvement of the vagus and chemoreceptive mechanisms in the respiratory response to adrenaline and noradrenaline it would seem that the responses must be due to the direct action of these substances (1) on the respiratory centre, or (2) on the peripheral neuromuscular mechanisms concerned with respiration.

Direct action of adrenaline on respiratory centre

The result of direct vertebral intra-arterial injections of adrenaline in the present study was negative, as were similar experiments in man (Coles, Duff, Shepherd & Whelan, 1956). (McDonald & Potter's (1951) observations on the cerebral flow in the rabbit show that a slow injection into one vertebral artery might reach the corresponding side of the medulla only. To exclude the possibility that adrenaline would not stimulate the centre if unilaterally distributed three experiments were carried out in cats, in which bilateral injections were made with similar negative results.) Adrenaline can cause constriction of the cerebral vessels in the monkey (Dumke & Schmidt, 1943)

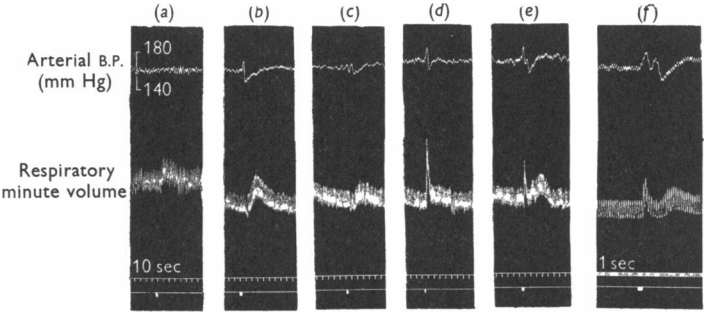

Fig. 9. To demonstrate that vertebral intra-arterial injections of adrenaline in the anaesthetized cat reach the respiratory centre. The respiratory responses are shown to injections of: (*a*) 0·5 ml. 0·05 N-HCl into the femoral vein; (*b*) 1 μg adrenaline into the femoral vein; (*c*) 1 μg adrenaline into the vertebral artery; (*d*) 0·5 ml. 0·005 N-HCl into the vertebral artery; (*e*) and (*f*) 1 μg adrenaline in 0·5 ml. 0·005 N-HCl injected into the vertebral artery. *Note*: (1) the immediate gasp due to the acid in records (*d*), (*e*), (*f*); and (2) the delay of hyperpnoea in (*e*) and (*f*) which is approximately equal to the delay of the intravenous response.

and in the spinal cord of the rabbit (Field, Grayson & Rogers, 1951), and it was therefore questionable whether the intravertebral injection in this study reached the respiratory centre. The following evidence suggests that there can be little doubt that these arterial injections did reach the respiratory centre: 0·5 ml. 0·005 N-HCl injected into the artery either alone or together with the adrenaline caused an immediate gasp (Fig. 9) which was of the same magnitude as that following the intravenous injection of 0·5 ml. 0·05 N-HCl. Gray & Paton (1949) found that sodium chloride was also diluted about tenfold, measured by a conductivity method, during its passage from the femoral vein to the carotid artery. It was on this basis that the value of the first vertebral intra-arterial injection was chosen: one-tenth the effective intravenous dose was found to be ineffective intra-arterially as were the smaller quantities tried, down to one-two-hundredth of the intravenous dose. No positive result on respiration was ever obtained until a dose was given equal to that producing

the hyperpnoea characteristic of adrenaline when injected intravenously. The latent period of the response obtained was equivalent to, and the magnitude rather smaller than, that following intravenous injection, and it is probable that it was due to some adrenaline which had emerged from the cerebral vessels and was circulating as though given by the intravenous route. Similar results were obtained for the inhibitory action of noradrenaline, following vertebral intra-arterial injection.

Discrepancy between the effects of drugs given intravenously and intra-arterially is well known. Schmidt (1929) first showed that adrenaline apnoea did not occur after the vertebral intra-arterial injection of the drug in dogs, suggesting an absorption or destruction of adrenaline by cerebral tissue before it could appear in the general circulation and cause the rise in arterial blood pressure necessary to initiate the reflex apnoea. The action of adrenaline on muscle blood flow in man also depends upon the route of injection; continuous intra-arterial injections cause a transient dilatation only, due to the direct action of adrenaline on the blood vessels (Barcroft & Swan, 1953), while continuous intravenous infusions cause a transient dilatation which is followed by a sustained dilatation. Hildes, Purser & Sherlock (1949) could demonstrate no change in muscle glycogen or in blood lactate during the continuous intra-arterial infusion of adrenaline to the leg in man, but a well-marked reduction in muscle glycogen was found to occur during intravenous infusion, together with a rise in blood lactate (Hildes, Sherlock & Walshe 1949). Barcroft, Peterson & Schwab (1951) observed that intravenous infusions of adrenaline increased Parkinsonian tremor in man; since intra-arterial infusions to the limbs concerned were without effect on the tremor, they concluded that the adrenaline was acting centrally.

Action of adrenaline on peripheral neuromuscular mechanism

It is unlikely that adrenaline or noradrenaline are affecting respiration by a direct action on the skeletal muscles concerned, for in the present experiments the contraction of the maximally stimulated gastrocnemius muscle was unaffected by the doses used. This is in agreement with many previous observations since Oliver & Schäfer (1895) originally showed that adrenal medullary extracts potentiated the contraction of unfatigued skeletal muscle. Grüber (1922) also obtained large increases of twitch tension of indirectly stimulated muscle after the intravenous injection of big doses of adrenaline or after splanchnic stimulation. These results have been confirmed during the last ten years, for both adrenaline and noradrenaline (Goffart & Brown, 1947; West & Zaimis, 1949; Goffart, 1952, 1954); the responses have not been so striking as those obtained earlier and there has been little agreement as to the mode and site of action. Bowman (1956) has extended the observations to different types of muscle and finds that both adrenaline and noradrenaline

increase the tension in those muscles containing predominantly white fibres, such as the tibialis anterior, and decrease the tension in muscles containing predominantly red fibres, such as the soleus. The doses Bowman used were comparable with those used in the present experiments, and in view of this contrast between the effects on different types of muscle it would have been more appropriate to study the response of the diaphragm and intercostal muscles rather than of the gastrocnemius. Goffart & Ritchie (1952) showed that adrenaline and noradrenaline increased the twitch tension in the isolated rat diaphragm.

So far there is therefore no conclusive evidence for the site of action of adrenaline or noradrenaline as they influence respiration in the anaesthetized animal. The results following the vertebral intra-arterial injection of these amines suggest two further possibilities, namely (1) that they act only in the thoracic region and do so after the injections have escaped from the cerebral circulation, or (2) that they are converted into an active substance outside the cerebral circulation which stimulates the respiratory centre when it reaches the medulla.

Action of adrenaline in thoracic region

If the amines stimulated receptors in the heart or lungs the afferent fibres would have to be sympathetic in origin, for all other innervation to the thorax has been excluded in these experiments. The receptors of Gruhzit, Freyburger & Moe (1954) in the thoracic aorta, innervated by fibres running in the thoracic dorsal roots, must be excluded, as must those of Ballin & Katz (1941) in the right heart. Hypothetically the amines could stimulate receptors in the heart and lungs either directly or indirectly by causing local changes in the pulmonary vascular bed, when the resulting accumulation of CO_2 or depletion of oxygen might be the effective stimulus. The latter explanation would again seem unlikely, for adrenaline hyperpnoea is not abolished by dibenyline and the site of action of adrenaline and noradrenaline on the pulmonary vasculature in the experimental animal is uncertain and the responses unpredictable (Franklin, 1932; Gaddum & Holtz, 1933; Daly, Foggie & Hebb, 1940; von Euler & Liljestrand, 1947; Edwards, 1951; Smith & Coxe, 1951).

In man, adrenaline and noradrenaline increased the mean pulmonary arterial pressure (Goldenberg, Pines, Baldwin, Greene & Roh, 1948), but it was not known whether this was due to vasoconstriction in the pulmonary bed.

B. Folkow & J. R. Pappenheimer (personal communication) found that injections of large doses of adrenaline in artificially ventilated dogs reduced the arterial oxygen saturation and increased the arterial carbon dioxide content; further, the oxygen content of the expired air was increased and the carbon dioxide content decreased. Both these changes indicated impaired ventilation perfusion ratios and were implied in Konzett & Hebb's (1949) results, for they found that both adrenaline and noradrenaline increased the

vascular resistance and diminished the lung volume in isolated perfused dog's lungs. Folkow has suggested that it is the alteration in the gaseous composition of the blood which might act as the stimulus causing the hyperpnoea.

Action of adrenaline after it is converted into or it has released some other substance

If adrenaline or noradrenaline are effective in stimulating respiration after being converted into another substance it appears from the experimental evidence that the conversion cannot take place in the cerebral circulation and may be confined to the heart and lungs. Removal of the abdominal viscera either singly or completely did not influence the responses, but if the conversion is a general property of the majority of tissues the response could still occur in the 'head and thorax' preparation, without any special property being assigned to the thoracic region. (The large rise in arterial pressure observed, as the balloons were inflated in the inferior vena cava and the abdominal aorta just above the diaphragm to obtain the 'head and thorax' preparation, has previously been described by Barcroft (1931).) The persistence of adrenaline hyperpnoea after removal of the abdominal viscera excludes the possible involvement of Bean's (1952) visceral chemoreceptors in the response, and its persistence in the absence of the liver decreases the importance of the possible role of the release of potassium ions from the liver as being responsible for the action of adrenaline (D'Silva, 1949). If the responses in the present experiments are due to the conversion of adrenaline into another substance this would correspond with the suggestion made by Whelan (1952) that the sustained vasodilatation in human muscle during intravenous infusion was due to the release by adrenaline of another chemical substance. Final evidence for its existence must be obtained by cross-circulation experiments. It is interesting to note that Brown (1916), perfusing the dog's medulla through the vertebral artery with a simple pressure bottle and very diluted defibrinated blood, obtained either a stimulation or an inhibition of respiration when adrenaline was added to the blood. However, when the perfusate containing the adrenaline was circulated a second time a stimulation of respiration was always obtained. Heymans & Heymans (1926) found that adrenaline added to the arterial blood in the isolated perfused dog's head preparation sometimes stimulated respiration, but never caused apnoea.

The relationship between the respiratory responses to adrenaline or noradrenaline in the anaesthetized animal and in conscious man

Any discussion as to the inter-relationship between the various results obtained in the anaesthetized animal and their relationship with those obtained in man is at present purely speculative. However, certain correlations sug-

gested in previous sections may be amplified. The first is the suggested resemblance between the sigh seen after the intravenous injection of adrenaline, in newly and lightly anaesthetized animals, and the abrupt onset of respiration in man in response to adrenaline infusions (Whelan & Young, 1953) which corresponds with a 'spike' in the pulse rate, arterial blood pressure and forearm blood flow responses (Young, 1956). These abrupt responses may be due to the direct action of adrenaline itself upon receptors which adapt quickly, as has been shown for the transient dilator response of the muscle blood vessels in man (Barcroft & Swan, 1953); these receptors are probably very sensitive to anaesthesia, for sighs were not detected in the more deeply anaesthetized animal and the 'spike' response was not observed in anaesthetized man (H. E. de Wardener & I. M. Young, unpublished). The absence of the abrupt onset of respiration under anaesthesia may be due to the accumulation of CO_2, for the 'spike' was reduced in human experiments when noradrenaline was infused during inhalation of high CO_2 mixtures (Young, 1956); alternatively, it may be due to the depressant action of the anaesthetics themselves. It is interesting to note that, in the one sleeping subject studied, the onset of respiration in response to an adrenaline infusion was abrupt (Whelan & Young, 1953).

The second correlation between the observed hyperpnoea in conscious man and in the anaesthetized animal is that the more sustained responses may be due to the release of a metabolic product, another hormone, or to a breakdown product of adrenaline itself. Whelan (1952) has shown that this explanation might account for the sustained dilation in human muscle, and the discussion on page 388 suggests that a similar explanation might apply to the observations on respiration in the anaesthetized animal.

The receptors for the sustained response may be the same as those responsible for the abrupt response but reacting differently to the second stimulus, or different receptors may be stimulated. Nevertheless, the receptors for the circulatory responses do not adapt quickly, neither do those responsible for the respiratory response when the CO_2 tension is above a critical level. This threshold was not determined, but the poorly sustained response to noradrenaline observed when subjects were breathing air and 2% CO_2 in air, was converted into a sustained response when mixtures containing 4% CO_2 or more, in air, were inhaled (Barcroft *et al.* 1956); there were comparable falls of CO_2 tension with 2% CO_2 and the higher mixtures, but the absolute level reached was lower when 2% CO_2 was inhaled. In addition, continuous intravenous infusions of adrenaline in the anaesthetized cat produce a sustained response; it is likely, but not proven, that this is also due to a raised alveolar of CO_2 tension. The administration of 5% CO_2 for a short period in the anaesthetized cat and rabbit abolishes the respiratory responses to adrenaline but in the rabbit this effect is readily reversible when the CO_2 administration

ceases. CO_2, therefore, would appear first to enhance the activity of the receptor for the sustained respiratory response and when in excess to depress it.

The receptors responding to the substance giving the sustained response to respiration are not quite so robust as those responsible for the vascular responses. In seven out of nineteen experiments in conscious man breathing high CO_2 mixtures the response to noradrenaline was beginning to fall off during the last 5 min period of the 15 min infusion; this may in part be accounted for by the reduced alveolar CO_2 tension (Barcroft *et al.* 1956). Further, adaptation of these receptors would seem to occur in the experimental animal, for increasing amounts of both amines have to be given to elicit a comparable respiratory response as the duration of anaesthesia proceeds. This adaptation might have been brought about by the continuous release of adrenaline by the suprarenal medulla, under the stress of the anaesthesia and experimental procedure, with a resulting tachyphylaxis. Elliott (1912) demonstrated that the adrenaline content of the suprarenal medulla fell during ether anaesthesia in the dog, and the changes in acid-base equilibrium observed in children under cyclopropane anaesthesia are similar to those observed during the administration of adrenaline infusions (Bunker, Brewster, Smith & Beecher, 1952). This tachyphylaxis of the respiratory responses to adrenaline has been noted by nearly every observer in the field, and Schmidt (1929) also found that it occurred for the adrenaline apnoea response. Late in an experimental period the tachyphylaxis is probably due to the depressant action of CO_2 accumulation.

Mention may be briefly made of the inhibitory response to adrenaline in the decerebrate cat, the inhibitory response preceding the stimulation with adrenaline, and the inhibitory response described for noradrenaline, in the anaesthetized cat and dog. There is no reason to suppose that these are actions on different receptors. In the decerebrate cat the reversal may be due to the absence of the influence of a higher centre on the medulla, and the small inhibition frequently observed before the stimulation of respiration by adrenaline is analogous to the dual action which nicotine has on ganglia, as pointed out by Barcroft & Swan (1953).

Lastly, the negative results obtained by Coles *et al.* (1956), who gave vertebral intra-arterial infusions of adrenaline or noradrenaline in conscious man, are in accord with the negative results obtained with similar injections in the anaesthetized animal and indicate that the latter were not necessarily due to the result of the depressant action of the anaesthesia.

The possible role of adrenaline and noradrenaline in the respiratory response to stress

The suggestion that adrenaline and noradrenaline are released from the suprarenal medulla and adrenergic nerve endings during stress, and particularly

that they may influence respiration during exercise, is not new. But unequivocal evidence that there is a raised blood level or an increased urinary excretion during exercise must be obtained before this possibility can be considered.

Increased catechol output occurs in animals, as in man, only under conditions of considerable stress (von Euler & Hellner, 1952); Wada, Seo & Abe (1935*a*, *b*) found that moderate exercise or the ingestion of cold water in unanaesthetized dogs did not increase the medullary secretion of catechols, measured as adrenaline, in the suprarenal venous blood. However, either severe physical exercise associated with fatigue or immersion in cold water resulted in a marked rise in catechol secretion.

The output of adrenaline and noradrenaline from the suprarenal medulla in the anaesthetized cat at rest and under stress has been measured by collection of suprarenal venous blood (Kaindl & von Euler, 1951; Duner, 1953; von Euler & Folkow, 1953; Folkow & von Euler, 1954) with subsequent biological assay on the cat's blood pressure and fowl's caecum; and by Celander (1954) using the response of the denervated nictitating membrane in the stressed cat to indicate the level of excretion from the suprarenal glands. Increased excretion of adrenaline and noradrenaline was observed after such stimuli as carotid occlusion, asphyxia, splanchnic and sensory nerve stimulation and hypothalamic stimulation. The most effective stimulus was asphyxia and Celander estimated that 1 μg adrenaline was released per minute. This value was, however, only found in the terminal stages of asphyxia, and Folkow (1955) has suggested that 1 μg adrenaline and noradrenaline is a large dose for a single injection in a cat. The doses, 0·05–0·25 μg/kg, required to produce respiratory responses in a sensitive preparation in the present experiments fall well below Folkow's 'large dose'.

SUMMARY

1. Experiments in the anaesthetized animal demonstrate that the respiratory response to intravenously administered adrenaline or noradrenaline are independent of the integrity of the vagus, the carotid and aortic buffer regions, the spinal cord below the level of the eighth cervical vertebra and the entire visceral contents. The action of both amines is widespread throughout the body, and it is possible that their effect on respiration is the result of a summation of stimuli and that the removal of one, or even several together, would not abolish the respiratory response.

2. Vertebral intra-arterial injections of the amines do not influence respiration. This does not entirely exclude the possibility that they might act directly on the respiratory centre. In support of the hypothesis that the action of the amines on respiration when given intravenously is partly a direct one on the respiratory centre itself, are the following observations; the inhibition of respiration preceding an adrenaline hyperpnoea in the cat and the dog;

reversal of the adrenaline hyperpnoea—an inhibition of respiration—in the decerebrate cat; the inhibition of respiration by noradrenaline in the cat and dog but a stimulation of respiration by noradrenaline in man and in the rabbit. The phenomena would suggest that there has been an alteration in balance between excitatory and inhibitory states in the respiratory centre.

3. It is unlikely that the respiratory response to adrenaline in the anaesthetized animal is secondary to vasoconstriction in the respiratory centre or any other receptor causing a reflex response, for the hyperpnoea persists after dibenyline. However, one explanation of the discrepancy between the results of intravenous and intra-arterial injection is that adrenaline stimulates respiration after it has been converted into another substance. If this is true, then it may be this new substance, which is not antagonized by the blocking agent but which may, nevertheless, be causing vasoconstriction in the receptor area.

My thanks are due to Professor Henry Barcroft for suggesting the problem.

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