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ANALYSIS OF CARDIOVASCULAR RESPONSES EVOKED FOLLOWING CHANGES IN PERIPHERAL CHEMORECEPTOR ACTIVITY IN THE RAT

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SUMMARY

1. Comparisons have been made between rats anaesthetized with pentobarbitone and Saffan (Glaxovet), of respiratory and cardiovascular changes evoked by (1) brief stimulation of carotid body chemoreceptors (c.b.); (2) systemic hypoxia induced by N_2 breathing for 5 s; (3) brief unloading of peripheral chemoreceptors with dopamine; and (4) O_2 breathing for 10 s. The results are discussed in relation to responses reported in other species.

2. Under pentobarbitone, c.b. stimulation evoked hyperventilation, tachycardia, and vasoconstriction in hindlimb muscle and renal and mesenteric circulation. The effects of vagotomy and/or of holding ventilation constant indicated that the primary cardiac response to c.b. stimulation was bradycardia which could be overcome by tachycardia, due to a reflex mediated by pulmonary stretch receptors with vagal afferents and to other secondary effects of hyperventilation. However, reflex vasodilatation initiated by hyperventilation did not modulate the chemoreceptor-induced peripheral vasoconstriction.

3. Under light pentobarbitone, N_2 evoked a similar pattern of response to c.b. stimulation, except that the tachycardia apparently also reflected the known effects of increased central inspiratory drive and central nervous hypoxia on cardiac vagal and sympathetic activity. However, under deep pentobarbitone or after guanethidine, N_2 induced generalized vasodilatation. It is proposed that these responses reflected the local vasodilator actions of hypoxia.

4. Under light Saffan anaesthesia, both c.b. stimulation and N_2 evoked the autonomic components of the alerting stage of the defence response which includes tachycardia and vasodilatation in hindlimb muscle, which are not secondary to hyperventilation, with renal and mesenteric vasoconstriction, pupillary dilatation and exophthalmus. However, under deep Saffan anaesthesia, c.b. stimulation and N_2 produced the patterns of response they each evoked under deep pentobarbitone. It is proposed that light Saffan anaesthesia allows chemoreceptor stimulation to activate the defence areas and that under such conditions the primary response to c.b. stimulation and direct effects of hypoxia may be overridden.

5. Under pentobarbitone or Saffan, the hypoventilation induced by I.V. dopamine and by O_2 indicated that almost 50% of eupnoeic ventilation was due to drive from peripheral chemoreceptors. This drive apparently played no significant role in setting

the baseline level of heart rate, but could account for 10% of total peripheral resistance and of the baseline level of arterial pressure under Saffan, rather less under pentobarbitone.

INTRODUCTION

In recent years the rat has become increasingly popular for studies of the reflex and central control of the circulation, and yet there has been no analysis of the cardiovascular response engendered in this species by peripheral chemoreceptor stimulation. The responses of the rat cannot be predicted from studies on other species, for there is considerable variation between species. Thus, in cats and dogs anaesthetized with chloralose or barbiturates the primary cardiovascular response evoked by stimulation of peripheral chemoreceptors is bradycardia and peripheral vasoconstriction (Daly & Scott, 1962; MacLeod & Scott, 1964; Little & Oberg, 1975; Daly, Litherland &Wood, 1983*a*). However, in the spontaneously breathing dog this response may be overcome by tachycardia and vasodilatation which is most pronounced in skeletal muscle. These effects are secondary to the chemoreceptor-evoked hyperventilation and are predominantly due to a reflex initiated by stimulation of lung stretch receptors whose afferents run in the vagi (Daly & Scott, 1962), augmented by the effects of the fall in arterial P_{CO_2} (Daly & Scott, 1963); while the tachycardia is in part due to the effects of the increased central inspiratory drive (Daly, 1984). Such respiratory-dependent effects are much less pronounced in the cat; bradycardia predominates except when the evoked hyperventilation is particularly strong (MacLeod & Scott, 1964) and vasodilatation elicited by hyperventilation attenuates, but does not overcome the primary vasoconstriction (Daly, Litherland &Wood, 1983*a*, *b*). In the rabbit, respiratory-dependent effects are even less pronounced in that bradycardia predominates even during intense chemoreceptor stimulation (Crocker, Johnson, Korner, Uther & White, 1968). On the other hand, in primates the central effects of increased central inspiratory drive upon heart rate are particularly marked (Daly, Korner, Angell-James & Oliver, 1978).

In addition, other factors may determine the final response to chemoreceptor stimulation. In the cat, at least, the commonly used anaesthetics, barbiturates and chloralose, prevent activation of the brain-stem defence areas from afferent inputs like the amygdala and cutaneous nociceptors (Timms, 1981; Hilton & Marshall, 1982). By contrast, the steroid anaesthetic alphaxalone–alphadalone (Althesin, Glaxo, or its veterinary equivalent Saffan, Glaxovet) can be given to the cat in a dose which produces adequate anaesthesia and yet allows the autonomic components of the alerting stage of the defence response (visceral alerting response) to be evoked not only by stimulation of the amygdala or cutaneous nociceptors (Timms, 1981), but also by peripheral chemoreceptor stimulation (Hilton & Marshall, 1982). This visceral alerting response includes renal and mesenteric vasoconstriction, but tachycardia and vasodilatation in skeletal muscle which are not secondary to the accompanying hyperventilation (Hilton & Marshall, 1982). When evoked by chemoreceptor stimulation it is superimposed upon the primary and secondary effects described above and can predominate over them if the chemoreceptor stimulus is sufficiently strong (Hilton & Marshall, 1982; Marshall, 1986).

In the present study analysis has been made of the heart rate and regional vascular resistance changes evoked in the rat by stimuli applied selectively to the carotid body chemoreceptors and by systemic hypoxia produced by a short period of N_2 inhalation. Since a previous study indicated that the pressor response to carotid occlusion in rats anaesthetized with pentobarbitone includes a component which is initiated by carotid chemoreceptors and dependent on the integrity of the hypothalmic defence area (Lopes, Cipola-Neto & Rocha Silva, 1977), this raised the possibility that in the rat, barbiturate anaesthesia does not depress transmission through the defence areas to the same extent as in the cat. On the other hand, it is not known whether anaesthesia induced by alphaxalone–alphadalone in the rat can preserve transmission through the defence areas as in the cat. Thus it seemed particularly important to make a comparison of the effects of chemoreceptor stimulation in rats anaesthetized with pentobarbitone and with alphaxalone–alphadalone.

In previous studies, O_2 inhalation or administration of dopamine into the circulation has been shown to inhibit normoxic chemoreceptor activity; the magnitude of hypoventilation induced indicated that both in awake and pentobarbitone-anaesthetized rats, approximately 50% of spontaneous respiration is sustained by peripheral chemoreceptor drive (Favier & Lacaisse, 1978; Cardenas & Zapata, 1981, 1983). Recent evidence indicates that peripheral chemoreceptor stimulation can, via the pathway from the defence areas and via a more direct route from nucleus tractus solitarius, activate those neurones in nucleus paragigantocellularis of the ventral medulla whose activity seems to provide the major sympatho-excitatory drive for normal levels of arterial pressure (see Marshall, 1986, for references). Thus it has become of particular interest to establish the extent to which the normal level of arterial pressure is dependent on tonic activity of peripheral chemoreceptors. Attempts were made to do this in the present study by using O_2 and dopamine.

Some of the results have already been reported (Marshall, 1984).

METHODS

The experiments were performed on male and female rats of 270–360 g body weight (mean 314 g). Group I comprised twenty-seven rats in which anaesthesia was induced with ether or ethyl chloride and maintained with sodium pentobarbitone (50–60 mg kg^{-1} I.M., followed by supplementary doses of 6–8 mg kg^{-1} I.V.). Group II comprised twenty rats in which anaesthesia was induced with halothane and O_2 and maintained with an initial I.V. injection of Saffan, 3–4 mg kg^{-1}, followed by continuous I.V. infusion of Saffan at a rate of 8–18 mg kg^{-1} h^{-1} during surgery and 5–8 mg kg^{-1} h^{-1} during the experimental period. In all experiments the level of anaesthesia was judged by testing somatic reflexes: during surgery a corneal reflex was present but there was no withdrawal reflex, whereas during the experimental period withdrawal reflexes were present but there were no spontaneous movements and cardiovascular and respiratory variables were stable. In both groups of animals, anaesthetic agents were administered via a jugular vein and other pharmacological agents via a femoral vein. Arterial pressure was recorded via a pressure transducer (Bell & Howell) from a cannula inserted through a femoral artery into the dorsal aorta. Heart rate was derived from arterial pressure by a rate meter (Ormed). Blood flow was recorded from a femoral artery and either the left renal artery (twenty rats) or anterior mesenteric artery (fourteen rats) by means of cuff-type electromagnetic flow transducers and meters (Carolina, Medical Electronics Inc.). The femoral artery was approached from the medial aspect and the circulation

to the paw excluded by a stout ligature so that the recorded blood flow was mainly to skeletal muscle. The left renal and the mesenteric arteries were approached via the left flank, the incision being resealed after placement of the transducer. Zero flow was obtained at regular intervals during the experiment by temporary occlusion of the artery distal to the transducer. The transducers were calibrated *in vitro* by constant-flow perfusion. Vascular conductance for each vascular bed was computed on-line by a custom-built electronic divider which made a division of arterial flow by arterial pressure. A stainless-steel T-shaped cannula was placed in the trachea, the side arm was connected to a flow head (F10L) and Electrospirometer (Mercury, CS6) and used to record respiratory frequency and tidal volume. All variables were recorded on an 8-channel pen recorder (Devices M8).

Solutions were administered locally to the carotid body via a cannula which was inserted, with the aid of an operating microscope, through the left lingual artery into the external carotid artery and advanced so that the tip lay at the bifurcation of the common carotid artery. All branches of the common carotid artery except those which supplied the carotid body were ligated. To *stimulate* the chemoreceptors a solution of isotonic NaH_2PO_4 (0·208 M) diluted with isotonic saline as required (see Results) was injected in a volume of 0·05–0·1 ml over a period of 10–20 s (cf. Hilton & Marshall, 1982). In some experiments dopamine in saline was administered to *inhibit* chemoreceptor activity, either via the above cannula or via a cannula placed in the contralateral external carotid artery or I.V. In order to test responses evoked by short-lasting hypoxia or hyperoxia, 100% N_2 or O_2 (BOC) was administered via the respiratory flow head for 5 or 10 s respectively.

In five group I and four group II animals muscular paralysis was induced with gallamine triethiodide (Flaxedil; 10 mg kg^{-1}, I.V.) supplemented as necessary to prevent spontaneous respiratory movements. Thereafter artificial respiration was achieved via a pressure-controlled ventilator (Harvard Apparatus Ltd); respiratory rate was set at the spontaneous respiratory frequency, and delivery pressure was adjusted so as to maintain arterial pressure at pre-paralysis levels. Whilst paralysed each group I animal received supplementary doses of pentobarbitone at intervals equal to those found necessary to maintain anaesthesia during spontaneous respiration, each group II animal received Saffan at the same rate as in the period immediately preceding paralysis. The fact that adequate anaesthesia was maintained, was verified by the stability of heart rate, arterial pressure and regional vascular conductance. During paralysis responses induced by hypoxia and hyperoxia were tested by administering N_2 or O_2 for 10 or 15 s respectively via the inlet to the ventilation pump.

RESULTS

The magnitude of change in each variable is expressed as a percentage of the baseline level immediately before the stimulus. The time-to-peak of each response was measured from the onset of the stimulus. Responses evoked by selective stimulation of carotid bodies (c.b.), by N_2 and by O_2 breathing, were routinely tested in all group I and II animals at intervals of 5–10 min throughout the experimental period which lasted 4–6 h. Responses induced by intracarotid injection (I.C.) of dopamine were tested in five group I and three group II animals. The concentration of NaH_2PO_4 used for c.b. stimulation was usually between 10 and 50% of the stock isotonic solution and was chosen at the beginning of each experiment so that it would produce a peak increase in minute volume (V_e) of > 50%. The chosen concentration was then used throughout the experiment. Repeated tests on three animals showed that the responses evoked by NaH_2PO_4 could be mimicked by injection of saline equilibrated with CO_2 (another recognized chemoreceptor stimulant). Moreover, in four experiments section of the carotid sinus nerve abolished the cardiovascular and respiratory responses evoked by NaH_2PO_4, demonstrating that they were due to stimulation of carotid chemoreceptors (Hilton & Marshall, 1982).

Group I

Control levels of mean arterial blood pressure (A.B.P.), heart rate (H.R.), respiratory frequency (f_r) and tidal volume (V_t) are shown in Table 1; all variables tended to rise within the ranges shown during the 15–60 min periods between supplementary doses of pentobarbitone.

Carotid body stimulation evoked hyperventilation, an increase in A.B.P. and a tachycardia which was sometimes preceded by transient bradycardia (see below), together with renal, mesenteric and femoral vasoconstriction (Table 1 and Fig. 1). All of these variables reached the peak of their change in 8–12 s. Often the respiratory response included a gasp or augmented breath (an additional inspiratory effort at the peak of a normal inspiration: Davies, Dixon, Callanan, Husczuk, Widdicombe & Wise, 1978). In these cases the cardiovascular response was usually interrupted by a transient bradycardia of up to 20 beats min^{-1} and/or a depressor response (Fig. 1); apparently comparable augmented breaths and associated cardiovascular changes occurred spontaneously (Fig. 3; cf. Marshall & Metcalfe, 1986). The changing level of anaesthesia had no qualitative effect on the response evoked by c.b. stimulation, but the magnitude of the individual components increased within the ranges given, as the level became lighter.

By contrast, the pattern of response evoked by N_2 breathing for 5 s was qualitatively dependent on depth of anaesthesia (Fig. 2 and Table 1). Thus, after a supplementary dose of pentobarbitone, N_2 elicited hyperventilation, tachycardia, a *fall* in A.B.P., with peripheral vasodilatation that was most pronounced in femoral vasculature, these changes being achieved in 8–12 s. However, as the level of anaesthesia became lighter (i.e. between does of pentobarbitone), the evoked respiratory response increased and the vascular response first became biphasic (constriction then dilatation or vice versa) and eventually vasoconstriction predominated. At this stage there was hyperventilation, tachycardia, but A.B.P. *rose* while femoral, renal and mesenteric vascular conductance (F.V.C., R.V.C. and M.V.C. respectively) decreased. Thus the response to N_2 became qualitatively similar to that evoked by c.b. stimulation. Also, N_2, like c.b. stimulation, evoked augmented breaths with associated bradycardia and vasodilatation. At light levels of anaesthesia c.b. stimulation and N_2 also consistently elicited pupillary dilatation and movement of vibrissae (cf. group II).

Oxygen breathing for 10 s invariably induced hypoventilation (Fig. 3), so that V_e fell by 25–40% in 10–12 s. Meanwhile there was a gradual fall in H.R., rise in A.B.P. and a simultaneous decrease in F.V.C., R.V.C. and M.V.C., all of these changes reaching their maximum in 15–20 s. In some tests, particularly at light levels of anaesthesia, this pressor response was preceded by a transient decrease in A.B.P. of 5–10 mmHg.

Early experiments established that dopamine, 10^{-8}–10^{-6} g kg^{-1} I.V., induced a 40–45% fall in V_e. This was always followed by a slow rise in A.B.P. of up to 15 mmHg which was probably due to the direct vasoconstrictor action of the drug (see Discussion). In contrast to the results of Cardenas & Zapata (1981) it proved impossible to find a dose of dopamine which when given I.V. would induce hypoventilation without producing a pressor response. Thus, in later experiments dopamine was injected I.C. in an attempt to achieve a more selective effect on

chemoreceptors. In twenty-two tests on five animals 10–15 μg dopamine I.C. induced a 17–25% decrease in V_e in 10–12 s (see Table 1). In four tests on two animals this was accompanied by a transient but small fall in A.B.P. of 5–10 mmHg. However, in eight tests on three animals there was no obvious change in A.B.P., and in the

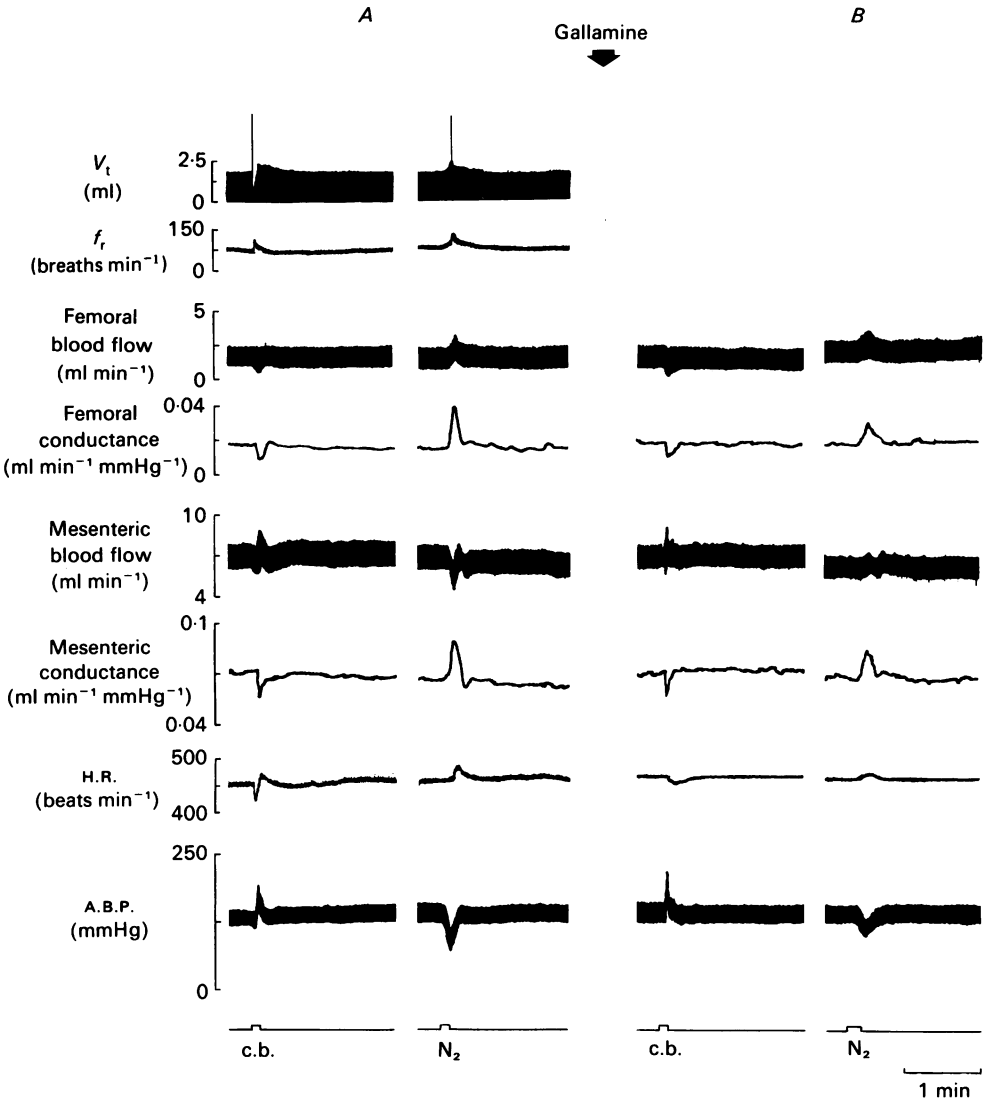

Fig. 1. Rat, pentobarbitone. Responses evoked by carotid chemoreceptor (c.b.) stimulation and nitrogen (N_2) during spontaneous (*A*), and constant artificial ventilation (*B*). Records from above down: respiratory tidal volume, respiratory frequency, blood flow and vascular conductance in femoral and mesenteric beds, heart rate and arterial pressure. Gallamine (10 mg kg^{-1}) was administered between *A* and *B*.

remaining ten tests on one animal there was a slow rise in A.B.P. of up to 10 mmHg (Fig. 3). Any changes in H.R. or in the regional vascular conductances were small and inconsistent. Responses evoked by dopamine were not noticeably affected by depth of anaesthesia.

Responses after vagotomy. Bilateral vagotomy produced the expected decrease in baseline f_r and increase in V_t, but V_e remained more or less constant (Table 1). The A.B.P. increased by 10–15 mmHg in sixteen animals and decreased by 5–10 mmHg in the remaining four animals. The H.R. generally decreased by 10–15 beats min^{-1} but

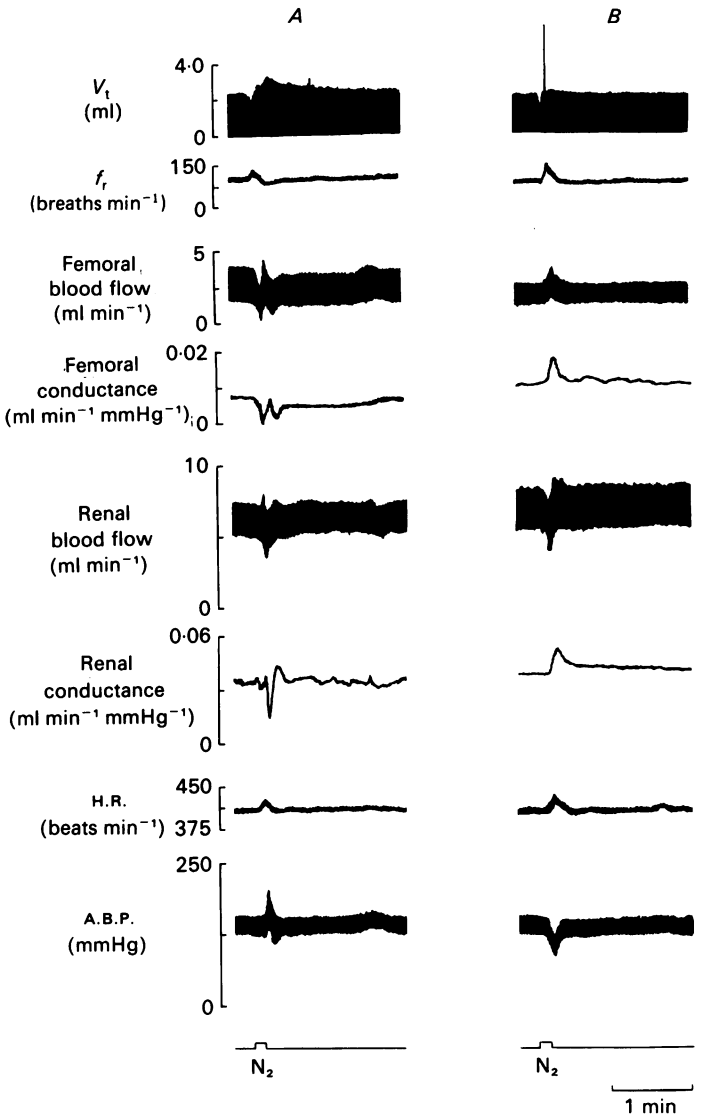

Fig. 2. Rat, pentobarbitone. Responses evoked by N_2 before (*A*) and after (*B*) a supplementary dose of sodium pentobarbitone (6 mg kg^{-1}, I.V.). Traces as in Fig. 1, except blood flow and vascular conductance in renal bed.

in two cases it increased by 5–10 beats min^{-1}. Thereafter, augmented breaths rarely occurred, either spontaneously or in response to c.b. stimulation or N_2 (cf. Marshall & Metcalfe, 1986). From these new baselines both c.b. stimulation and N_2 produced hyperventilation, of which an increase in V_t played a larger part than in the intact animal (Table 1). Vagotomy had no obvious qualitative or quantitative effect on the

TABLE 1. Responses evoked in group I animals before and after vagotomy

	Group I (pentobarbitone)					
	A.B.P. (mmHg)	H.R. (beats min^{-1})	f_r (breaths min^{-1})	V_t (ml)	F.V.C.	R.V.C., M.V.C.
Control	110–135	410–450	80–100	1·75–2·3		
Δ evoked by						
c.b.	↑20–35	↑10–15	↑20–30%	↑0–30%	↓25–50%	↓20–40%
N_2	↑25–50	↑15–25	↑45–80%	↑20–70%	↓25–40%	↓15–50%
After supplementary pentobarbitone						
Δ evoked by						
N_2	↓25–50	↑15–25	↑37–50%	↑20–40%	↑100–150%	↑35–40%
O_2	↓5–10*, ↑7–15	↓8–12	↓15–25%	↓10–20%	↓ < 10%	↓ < 10%
DA (I.C)	↓5–10*, ↑0–10	—	↓12–15%	↓5–20%		
	After vagotomy					
Control	120–145	400–435	45–60%	3·5–4·0		
Δ evoked by						
c.b.	↑25–40	↑5–10	↑35–40%	↑20–40%	↓20–50%	↓23–45%
N_2	↑30–55	↑10–18	↑50–60%	↑30–40%	↓25–45%	↓20–50%
After supplementary pentobarbitone						
Δ evoked by						
N_2	↓30–60	↑8–20	↑50–55%	↑30–40%	↑100–150%	↑30–40%
O_2	↓5–15, ↑15–20	↓10–15	↓15–25%	↓15–23%	↑ < 10%, ↓25–30%	

Changes (Δ) evoked in A.B.P. and H.R. are given in mmHg and beats min^{-1} respectively; those in other variables are expressed as % of control; ↑ indicates increase, ↓ indicates decrease from control. * Denotes response not observed in all tests, see text for details. DA, dopamine.

pattern of cardiovascular response evoked by c.b. stimulation or N_2, except that in each animal the increase in H.R. evoked by each stimulus was smaller by 5–10 beats min^{-1}. Note that at deep levels of anaesthesia N_2 still evoked a fall in A.B.P. and marked increases in the regional vascular conductances (see Fig. 4 and Table 1).

The hypoventilation induced by O_2 was enhanced by vagotomy (Table 1); V_e fell by 35–50%. There was no obvious change in the magnitude of the accompanying

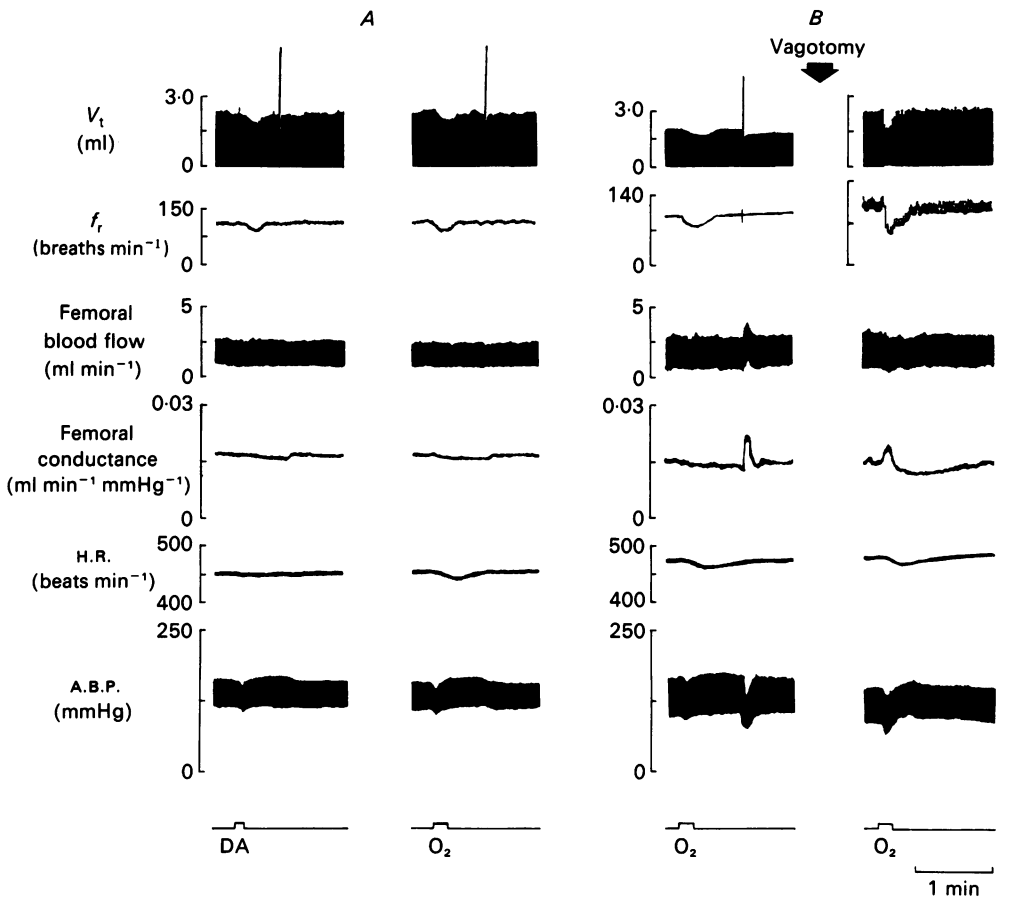

Fig. 3. *A*, rat, pentobarbitone. Responses evoked by I.C. dopamine (DA) and O_2 breathing. *B*, rat, Saffan. Responses evoked by O_2 breathing before and after vagotomy. Note spontaneous augmented breath and associated muscle vasodilatation in *B*. Traces as in Fig. 1.

bradycardia; the magnitude of the initial depressor response (when that occurred) was increased, but it never exceeded 15 mmHg and the accompanying increase in the regional vascular conductances was less than 10%. The later increase in A.B.P. and decrease in the regional vascular conductances were also larger (cf. group II, see Fig. 6). The effect of vagotomy on responses induced by dopamine was not studied.

Responses during paralysis and artificial ventilation. Tests were made on five animals with intact vagi. Changes in regional vascular conductance evoked by c.b.

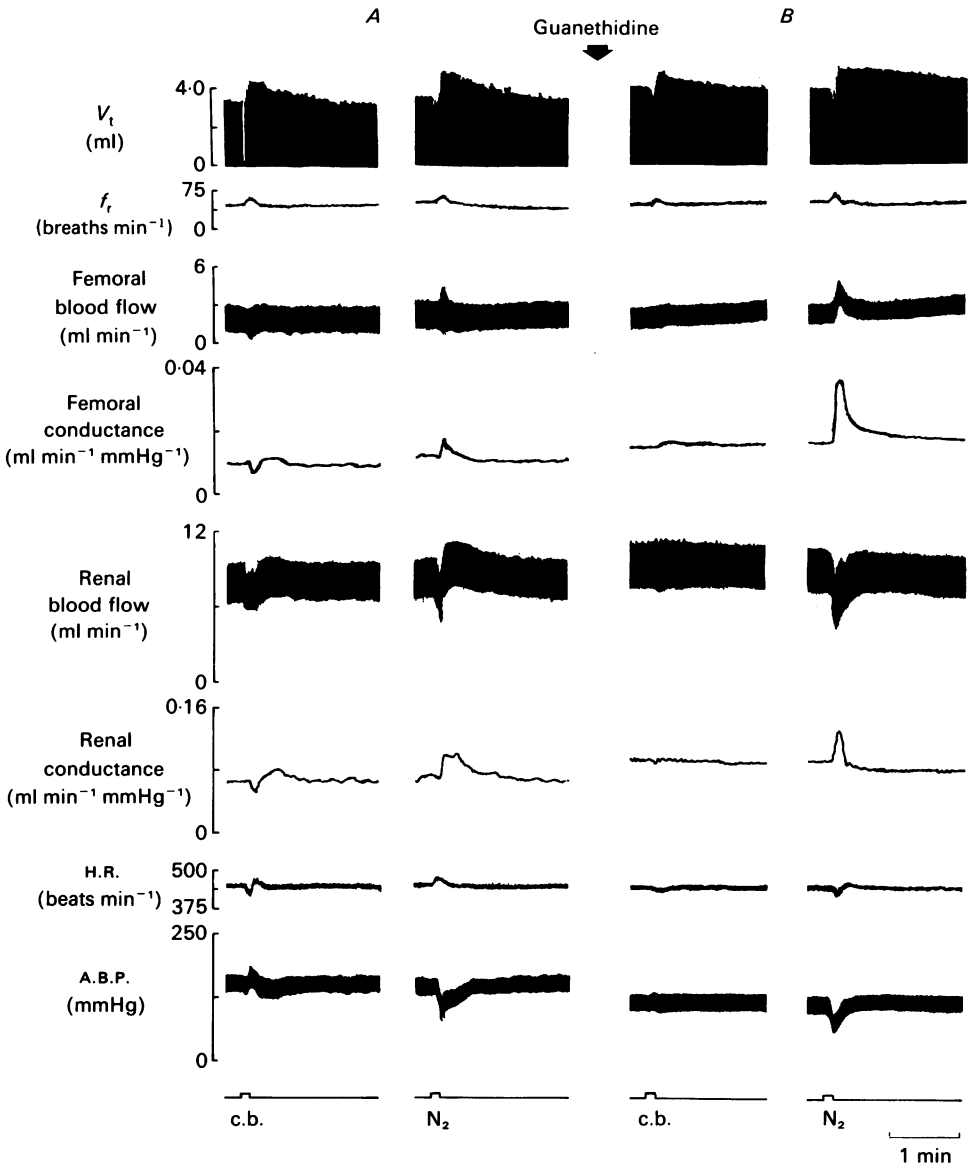

Fig. 4. Rat, pentobarbitone, vagotomized. Responses evoked by c.b. stimulation and N_2 before (*A*) and after (*B*) administration of guanethidine (10 mg kg^{-1}, I.V.). Traces as in Fig. 2.

stimulation were comparable in time course and magnitude to those evoked when the animal was allowed to hyperventilate (Fig. 1). However, in contrast to the tachycardia of the spontaneously breathing animal c.b. stimulation consistently evoked a decrease in H.R. of 5–15 beats min^{-1} (Fig. 1).

Despite the fact that the time course and magnitude of the change in P_{a,O_2} induced by N_2 administration must have been different from that induced during spontaneous

ventilation, the patterns of cardiovascular change evoked were similar, i.e. N_2 always evoked tachycardia, of 10–20 beats min^{-1}, but either a rise in A.B.P. and peripheral vasoconstriction under light anaesthesia, or (see Fig. 1) a fall in A.B.P. accompanied by increases in F.V.C. and in R.V.C. and M.V.C. (of 50–100% and 10–35% respectively) after supplementary pentobarbitone.

Responses evoked by O_2 were also qualitatively similar to those recorded during spontaneous respiration, viz. a slow pressor response accompanied by bradycardia, sometimes preceded by a depressor response. Responses to dopamine were not studied.

Responses after guanethidine. Guanethidine (10 mg kg^{-1}, I.V.) was given to four animals, two of which had been vagotomized. Heart rate stabilized within 10–20 beats min^{-1} either side of the control level, while A.B.P. stabilized below control, at 70–90 mmHg. Thereafter the respiratory responses evoked by c.b. stimulation and N_2 were fully comparable to those recorded in the control state (Fig. 4). However, the cardiovascular response evoked by c.b. stimulation was virtually abolished: H.R. fell by 5–10 beats min^{-1} in animals with intact vagi but showed no consistent change in vagotomized animals; any changes in F.V.C., R.V.C. and M.V.C. amounted to less than 10% from baseline. By contrast, N_2 consistently evoked a marked fall in A.B.P. of 45–75 mmHg in 8–12 s and simultaneous increases in F.V.C. (of 100–300%) and in R.V.C. and M.V.C. (of 50–100%) and were therefore much larger than those seen in the control state (Fig. 4). Heart rate always increased, by 5–10 beats min^{-1} in approximately 12–15 s, and returned to control over 1 min; this was often preceded by bradycardia of 5–10 beats min^{-1} even when vagi had been cut (Fig. 4). Further, in two animals this pattern of response was consistently followed by a slow decrease in F.V.C. (of 15–20%) and in R.V.C. and M.V.C. (10–15%) which lasted for 2–3 min (cf. Fig. 6); these changes were accompanied by a rise in A.B.P. of 15–40 mmHg above baseline and an obvious increase in pulse pressure.

The hypoventilation produced by O_2 or I.C. dopamine was not affected by guanethidine. However, the accompanying cardiovascular responses were changed in that neither stimulus induced an initial depressor response, but both consistently induced a slow rise in A.B.P. of 20–30 mmHg and a simultaneous decrease in the regional vascular conductances of up to 15%. As in the control state, the response to O_2 was accompanied by bradycardia of approximately 10 beats min^{-1}.

Group II

Control levels of mean A.B.P., H.R., f_r and V_t are shown in Table 2. Carotid body stimulation produced hyperventilation similar to that seen in group I. When the animal had reached the stable light level of anaesthesia chosen for the experimental period, the accompanying pattern of cardiovascular change comprised a rise in A.B.P. and H.R., with renal and mesenteric vasoconstriction, all of these changes reaching a peak in 10–12 s. In contrast to group I, the femoral vasculature showed initial constriction followed by pronounced dilatation (Figs 5 and 6, and Table 2). At this light level of anaesthesia the pattern of cardiovascular response evoked by N_2 was comparable with that evoked by c.b. stimulation, but the respiratory response was generally larger (Figs 5 and 6, and Table 2). As in group I, augmented breaths occurred spontaneously and in response to both c.b. stimulation and N_2 and were associated

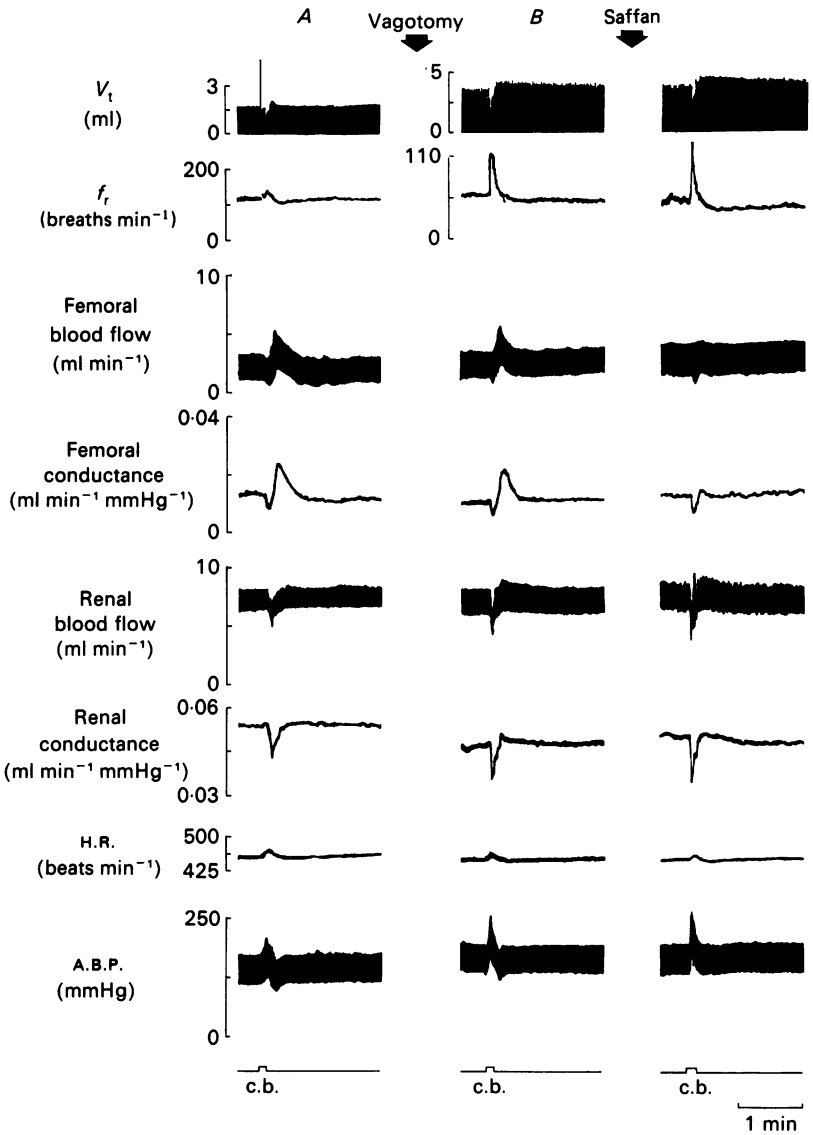

Fig. 5. Rat, Saffan. Responses evoked by c.b. stimulation with vagi intact (*A*), after vagotomy (*B*) and after bolus injection of Saffan (1 mg kg^{-1}, I.V.) in addition to the continuous infusion of Saffan (6 mg kg^{-1} h^{-1}). Traces as in Fig. 2.

with vasodilatation and sometimes bradycardia (Marshall & Metcalfe, 1986). Both c.b. stimulation and N_2 consistently evoked pupillary dilatation, exophthalmus, movement of the vibrissae and occasionally waving of the tail. The full pattern of response just described could also be evoked by heavy pinching of a paw.

By contrast, when the level of anaesthesia was increased by giving a bolus injection of Saffan (2–3 mg kg^{-1}, I.V.) in addition to the continuous infusion, and also when the animal was emerging from deep surgical anaesthesia, c.b. stimulation

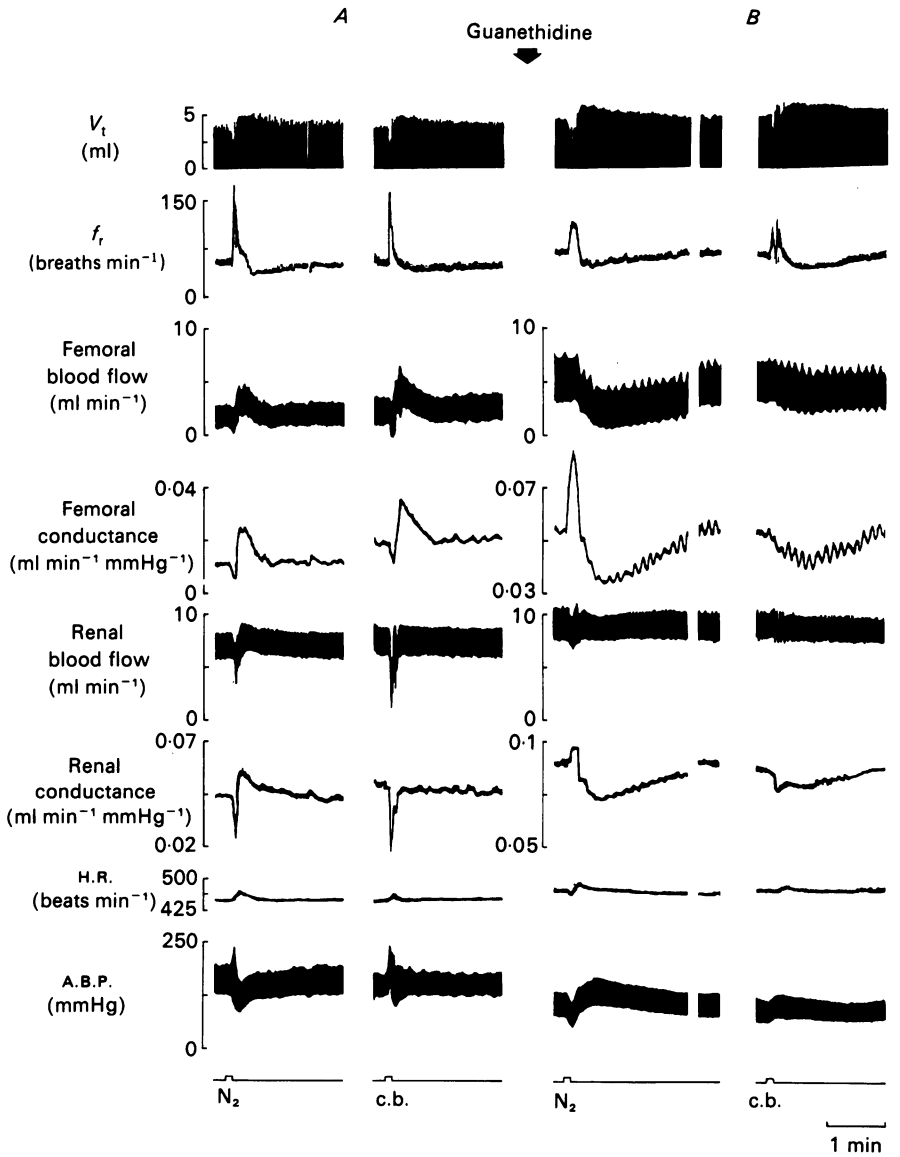

Fig. 6. Rat, Saffan, vagotomized. Responses evoked by c.b. stimulation and N_2 before (*A*) and after (*B*) guanethidine (10 mg kg^{-1}, I.V.). The break in the recordings of *B* lasted 1·5 min. Traces as in Fig. 2.

evoked a response which was indistinguishable from that evoked by c.b. stimulation in group I (compare Figs 1 and 5); notably there was vasoconstriction only in the femoral bed. Moreover, under these conditions N_2 evoked a response pattern which was indistinguishable from that evoked by N_2 in animals of group I which were under deep pentobarbitone, i.e. there was tachycardia, but a *fall* in A.B.P., accompanied by vasodilatation in renal, mesenteric and femoral beds (Table 2). Under these

TABLE 2. Responses evoked in group II animals before and after vagotomy. Abbreviations and symbols as in Table 1

	A.B.P. (mmHg)	H.R. (beats min^{-1})	f_r (breaths min^{-1})	V_t (ml)	F.V.C.	R.V.C., M.V.C.
Group II (Saffan)						
Control	120–140	375–460	80–110	1·7–2·0		
evoked by						
c.b.	↑25–55	↑10–35	↑12–28	↑ 0–25%	↓10–20, ↑100–200%	35–50%
N_2	↑25–65	↑15–40	↑12–35	↑15–45%	↓10–15, ↑130–250%	40–50%
After supplementary Saffan						
Evoked by						
c.b.	↑20–35	↑10–15	↑15–25%	↑0–20%	↓25–45%	↓15–35%
N_2	↓30–60	↑15–35	↑15–40%	↑10–35%	↑50–100%	↑35–50%
O_2	↓5–10*, ↑10–15	↓10–15	↓10–25%	↓10–20%	↓ < 10%	↓ < 10%
DA (I.C.)	↓5–10*, ↑10–15	—	↓10–15%	↓5–15%		
After vagotomy						
Control	125–145	370–445	45–55%	3·5–4·0		
evoked by						
c.b.	↑30–65	↑10–35	↑30–60%	↑12–30%	↓10–20, ↑100–200%	35–55%
N_2	↑30–60	↑10–35	↑35–200%	↑12–33%	↓10–15, ↑20–280%	35–50%
After supplementary Saffan						
evoked by						
c.b.	↑35–65	↑10–20	↑35–60%	↑10–25%	↓25–45%	↓15–30%
N_2	↓35–65	↑5–20	↑40–200%	↑20–30%	↑75–150%	↑35–50%
O_2	10–20, 15–20	10–15	15–25%	18–23%	↑10–15%	↓25–30%

conditions, both stimuli evoked pupillary dilatation and movement of vibrissae, but not exophthalmus or tail waving.

Oxygen induced a decrease in V_e of 25–50%, accompanied by a slow increase in A.B.P. and bradycardia of similar time course and magnitude to those seen in group I (Fig. 3 and Table 2). However, in contrast to group I, the pressor response was preceded in all tests by a transient fall in A.B.P. of 5–10 mmHg (Fig. 3).

Dopamine I.C. evoked a decrease in V_e of 15–30% (Table 2). In each of fifteen tests on three animals this was accompanied by a transient fall in A.B.P. of 5–10 mmHg but, as in group I, this was followed in five tests by a slow rise in A.B.P. of 10–15 mmHg.

Responses after vagotomy. In all twelve animals baseline f_r decreased while V_t increased following vagotomy; generally A.B.P. increased by 5–10 mmHg whereas H.R. fell by 5–15 beats min^{-1}. Vagotomy had no effect on the pattern of response evoked either by c.b. stimulation or N_2, except that the magnitude of the hyperventilation was somewhat larger (Fig. 5 and Table 2). There was no obvious change in the magnitude or time course of the tachycardia and femoral vasodilatation evoked by c.b. stimulation and N_2 under light anaesthesia (Fig. 5) or of the tachycardia and femoral, mesenteric and renal vasodilatation evoked by N_2 under deep anaesthesia (Table 2).

The magnitude of the hypoventilation induced by O_2 was greater than in intact animals (Fig. 3, cf. group I); V_e decreased by 40–53%. There was no qualitative change in the pattern of the cardiovascular response but each phase was larger (Table 2); the initial fall in A.B.P. generally ranged from 10 to 15 mmHg but was exceptionally 20 mmHg as in Fig. 3 and simultaneously the regional vascular conductances increased by 10–15%. Responses induced by dopamine were not examined.

Responses under paralysis and artificial ventilation. Tests were made on four vagotomized animals. The pattern of cardiovascular response evoked by c.b. stimulation was comparable in every respect with that seen during spontaneous respiration. Even though the change in P_{a,O_2} must have been different from that induced during spontaneous respiration, N_2 was still able to elicit a pattern of response comparable to that evoked by c.b. stimulation.

The pattern of response evoked by O_2 during artificial ventilation was also comparable to that evoked during spontaneous respiration (cf. group I). Responses to dopamine were not examined.

Responses after guanethidine. Five vagotomized animals were studied. Baseline A.B.P. stabilized at 65–90 mmHg and H.R. within 20–30 beats min^{-1} either side of control (cf. group I). Carotid body stimulation and N_2 evoked respiratory responses which were comparable to those of the control animal (Fig. 6) and both stimuli still elicited pupillary dilatation, exophthalmus, movement of vibrissae and sometimes tail waving. However, c.b. stimulation either evoked no cardiovascular change (two animals) or after a latency of approximately 10 s, a tachycardia of 15–25 beats min^{-1} and a slow decrease in F.V.C. (of 25–40%) and in R.V.C. and M.V.C. (of 12–20%), these returning to control in 2–3 min (Fig. 6). This latter pattern of response was also consistently produced by N_2, but initially F.V.C. and M.V.C. and R.V.C. always increased (by 60–80 and 10–30% respectively, Fig. 6).

The magnitudes of the hypoventilation induced by O_2 and by I.C. dopamine were comparable to those recorded in the control state. Both stimuli induced a slow increase in A.B.P. of up to 30 mmHg, which was greater than in the control state; this was never preceded by a depressor response (cf. group I). Oxygen still induced bradycardia of 10–15 beats min^{-1} (cf. group I).

DISCUSSION

Selective chemoreceptor stimulation under pentobarbitone

In rats anaesthetized with pentobarbitone, selective stimulation of carotid chemoreceptors evoked hyperventilation, tachycardia and vasoconstriction in hindlimb muscle and mesenteric and renal circulations and a rise in arterial pressure. Interpretation of the effect of vagotomy upon this response is not straightforward, since the fibres severed would have included not only afferents from pulmonary stretch receptors, whose activation in the dog can induce reflex tachycardia and peripheral vasodilatation (Daly & Scott, 1962), but afferent fibres from other receptors in heart and lungs and from aortic baroreceptors, as well as the vagal efferent supply to the heart. However, as vagotomy generally produced a fall in baseline level of heart rate and reduced the tachycardia evoked by chemoreceptor stimulation, this suggests that activity from pulmonary stretch receptors exerted a positive chronotropic effect during eupnoeic ventilation and that an increase in that activity caused by hyperventilation was partly responsible for the tachycardia observed on chemoreceptor stimulation. Since, when the vagi were intact but ventilation held constant, the response evoked by chemoreceptor stimulation was reversed to bradycardia, it may be concluded that influences other than lung stretch receptors but which are secondary to hyperventilation can induce tachycardia, although the primary cardiac response is bradycardia as in other species (see Daly, 1984). Given that a rise in P_{a,CO_2} induces bradycardia in the rat, apparently by a direct action on the heart (Lagneaux & Remacle, 1981; Hargreaves & Marshall, 1986), those secondary influences could have included the direct effect of a fall in P_{a,CO_2} resulting from hyperventilation, and possibly a reflex initiated by atrial stretch receptor stimulation caused by a respiratory-dependent increase in venous return (see Daly, 1984). The fact that the baseline level of heart rate was not always reduced by guanethidine may indicate that this drug was not fully effective in blocking cardiac sympathetic activity; however, the observation that after guanethidine when the vagi were intact, chemoreceptor stimulation evoked bradycardia, supports the idea that the primary response was vagally mediated and suggests that effects secondary to hyperventilation were predominantly mediated by sympathetic fibres.

As neither vagotomy nor maintenance of constant ventilation affected the peripheral vasoconstrictor responses evoked by chemoreceptor stimulation it seems that reflex vasodilatation elicited by pulmonary stretch receptor activation, which is strong in the dog but less marked in the cat (see Introduction), is weak or absent in the rat (cf. Marshall & Metcalfe, 1986). As the vasoconstrictor responses were abolished by guanethidine this indicates that they were mediated by sympathetic noradrenergic fibres.

N_2 inhalation under pentobarbitone

It might be expected that the influences exerted on the cardiovascular system during a given period of N_2 administration would, to an extent, be quantitatively dependent upon the P_{a,O_2} attained, which in turn would be dependent on the magnitude of the accompanying hyperventilation. However, the striking feature of the present results was that the pattern of response induced by N_2 was *qualitatively* determined by the level of anaesthesia, rather than by the ventilatory response. Thus, under light pentobarbitone, N_2 evoked a pattern of response which was essentially similar to that elicited by selective chemoreceptor stimulation, while under deep pentobarbitone, N_2 induced tachycardia, but generalized vasodilatation, and this was the case in the intact animal after vagotomy and during constant artificial ventilation.

The hyperventilation induced by N_2 was consistently greater than that induced by selective chemoreceptor stimulation, but this is understandable since the systemic hypoxia induced by N_2 would have activated both carotid bodies as well as any extracarotid chemoreceptors (Cardenas & Zapata, 1983). Judging by the effects of vagotomy, hyperventilation contributed to the tachycardia elicited by N_2 via the reflex effects of pulmonary stretch receptor stimulation. However, in contrast to selective chemoreceptor stimulation, N_2 induced tachycardia even when ventilation was held constant. This may be explained by a greater influence of increased central inspiratory drive on the vagal and sympathetic supply to the heart (Spyer, 1981) and/or to the ability of hypoxia of the central nervous system to increase cardiac sympathetic activity (Downing, Mitchell & Wallace, 1963). The bradycardia induced by N_2 after guanethidine, whether or not the vagi were intact, may be attributed to the direct depressant action of hypoxia on the heart (Krasney & Koehler, 1977). The later tachycardia seen under those conditions may have been due to the direct effect of a fall in P_{a,CO_2} secondary to the hyperventilation (see above). Alternatively, it may be ascribed to the β-adrenoreceptor action of catecholamines released from the adrenal medulla, since an increased output, principally of adrenaline, has been recorded as a reflex response to selective chemoreceptor stimulation (Critchley, Ungar & Welburn, 1973) and implicated in the response to systemic hypoxia (Uther, Hunyor, Shaw & Korner, 1970). Since guanethidine blocks the neuronal uptake mechanism for catecholamines as well as the release from sympathetic nerve terminals, but has little effect on release of catecholamines from the adrenal medulla, a given amount released from the gland could reach a higher concentration in the plasma after guanethidine and so have a greater effect on target organs (Maxwell, 1965).

Since the peripheral vasoconstrictor responses evoked by N_2 under light pentobarbitone, and the vasodilator responses evoked under deep pentobarbitone, were not affected by vagotomy and still occurred under artificial ventilation, they were apparently not modulated by dilatation secondary to hyperventilation (cf. the vascular response to selective chemoreceptor stimulation). The fact that after guanethidine or when the depth of pentobarbitone anaesthesia was increased, N_2 consistently induced vasodilatation in skeletal muscle and renal and mesenteric beds irrespective of the level of anaesthesia, suggests that these responses were not

neurally mediated. It may be concluded that peripheral vasoconstrictor responses evoked by N_2 reflected the reflex from peripheral chemoreceptors and that deep pentobarbitone unmasked dilatation induced by the direct action of hypoxia on the vascular smooth muscle or by vasodilator metabolites released as a consequence of tissue hypoxia (Daugherty, Scott, Dabney & Haddy, 1967).

The prolonged vasoconstriction in the regional vasculature which sometimes followed the dilator effect of N_2 when guanethidine had been administered, may be ascribed to the influence of circulating catecholamines. The ability of guanethidine to block the neuronal uptake mechanism as discussed above, may have ensured that catecholamines released from the adrenal medulla reached a high enough concentration in the plasma to overcome any β-mediated dilatation in skeletal muscle and to induce significant α-mediated vasoconstriction in all three vascular beds.

Carotid body stimulation and N_2 inhalation under Saffan

In rats under light Saffan anaesthesia, the pattern of response evoked both by selective chemoreceptor stimulation and N_2 contrasted strongly with that evoked under pentobarbitone for it included hyperventilation, tachycardia, renal and mesenteric vasoconstriction, but predominant vasodilatation in skeletal muscle. Neither the tachycardia nor the muscle vasodilatation were changed by vagotomy, nor by holding ventilation constant, and thus they were not secondary to the hyperventilation. However, they were accompanied by pupillary dilatation, exophthalmus, movement of the vibrissae and waving of the tail which characteristically accompany naturally evoked alerting behaviour in the conscious rat (Barnett, 1975). Indeed the pattern of response evoked by selective chemoreceptor stimulation and N_2 was fully comparable with the visceral alerting response evoked in the anaesthetized rat by electrical stimulation in the brain-stem defence areas (Yardley & Hilton, 1986). Thus it may be concluded that in the rat, as in the cat (Hilton & Marshall, 1982), light anaesthesia achieved with the steroid mixture alpaxalone–alphadalone (Saffan or Althesin) allows stimulation of peripheral chemoreceptors to activate the brain-stem defence areas. This view is reinforced by the observation that the response pattern evoked by chemoreceptor stimulation could also be elicited by heavy pinching of a paw, a stimulus which would be noxious in the conscious animal.

The early phase of the tachycardia and the peripheral vasoconstrictor responses evoked by selective chemoreceptor stimuli and N_2 were abolished by guanethidine, indicating that they were mediated by sympathetic noradrenergic fibres. Since after guanethidine, N_2 induced fairly rapid generalized vasodilatation, and both stimuli consistently induced rather slow, but long-lasting tachycardia and vasoconstriction in skeletal muscle and renal and mesenteric beds, these responses may be attributed respectively to the local effects of hypoxia and to the action of circulating catecholamines, as discussed above. The implication that responses induced by circulating catecholamines were more common under Saffan anaesthesia than under pentobarbitone is compatible with the fact that activation of the defence areas is known to cause release of adrenaline from the adrenal medulla (Grant, Lindgren, Rosen & Uvnas, 1958).

When the depth of Saffan anaesthesia was increased, both selective chemoreceptor

stimulation and N_2 evoked response patterns apparently comparable to those they evoked under deep pentobarbitone anaesthesia. Thus, it seems that when given in high doses, Saffan produces a state similar to that induced by even the lightest level of pentobarbitone anaesthesia used in the present study, in which normal activation of the brain-stem defence areas from afferent inputs is prevented. The defence areas may then be able to mediate only certain components of the visceral alerting response, which could explain the observation of Lopes *et al.* (1977) that lesions which included the hypothalamic defence areas attenuated the pressor response induced by chemoreceptor stimulation in pentobarbitone-anaesthetized rats. In the cat anaesthetized with Althesin the response evoked by chemoreceptor stimulation could be changed from that of the visceral alerting response to the primary bradycardia and generalized vasoconstriction expected in that species under pentobarbitone or chloralose anaesthesia (see Introduction), not only by increasing the depth of Althesin anaesthesia, but simply by reducing the strength of the stimulus presented to the chemoreceptors (Marshall, 1986). This led to the suggestion that the pattern of the visceral alerting response can be superimposed upon and predominate over the primary chemoreceptor response (Hilton & Marshall, 1982; Marshall, 1986). The present findings are consistent with that idea and indicate that the visceral alerting response can also predominate over the myocardial and local vasodilator effects of systemic hypoxia.

Effects of O_2 and dopamine

Intravenous dopamine which is known to inhibit normoxic chemoreceptor drive (Cardenas & Zapata, 1981) induced a short-lasting reduction in V_e of 40–45% in the pentobarbitone-anaesthetized rats. In intact rats, whether anaesthetized with pentobarbitone or Saffan, O_2 breathing caused a smaller reduction in ventilation amounting to only 25% in some animals, but after vagotomy O_2 also reduced ventilation by 40–50%. This may be explained because vagotomy induced an increase in baseline tidal volume and thus would have allowed a greater increase in alveolar P_{O_2} for a given period of O_2 breathing and a more effective inhibition of chemoreceptor activity. Given that the rat has little chemosensitive tissue served by the vagus (Cardenas & Zapata, 1981), both the dopamine and O_2 tests indicated that almost 50% of respiratory drive in pentobarbitone- and Saffan-anaesthetized rats was dependent on input from peripheral chemoreceptors, which is identical with previous estimates in awake and pentobarbitone-anaesthetized rats (Favier & Lacaisse, 1978; Cardenas & Zapata, 1981, 1983). The hypoventilation induced by I.C. dopamine indicated that one carotid body could account for up to 30% of total ventilation which is comparable with that estimated for the cat (Zapata & Zuazo, 1980).

If this chemoreceptor drive exerts a tonic effect on the cardiovascular system, then a neurally mediated change in cardiovascular variables might be expected to occur more or less simultaneously with dopamine- or O_2-induced hypoventilation. Neither I.V. nor I.C. dopamine produced any significant changes in heart rate. Both under pentobarbitone and under Saffan, O_2 induced a bradycardia which began during the hypoventilation but reached a maximum of 10–15 beats min^{-1} below control at least 5 s later, at approximately the same time as the peak of the accompanying pressor

response. Since *stimulation* of chemoreceptors in the spontaneously breathing rat evoked a short-latency, short-lasting tachycardia attributable to secondary effects of hyperventilation overcoming a primary bradycardia (see above), the initial part of the bradycardia induced by O_2 may reflect the effects of *unloading* the peripheral chemoreceptors. The later phase could be attributed to a baroreceptor reflex initiated by the slow rise in arterial pressure. However, as a bradycardia of similar time course and magnitude was still induced by O_2 after sympathetic tone had been inhibited with guanethidine and after vagotomy, it seems that the reflex effects of O_2 on heart rate could be mimicked by the direct effect exerted on the heart by hypercapnia secondary to the induced hypoventilation (see above). The only obvious conclusion is that in rats anaesthetized with pentobarbitone or Saffan, the extent to which the resting level of heart rate is dependent on normoxic chemoreceptor drive amounts at most to a few beats per minute.

The conspicuous effect of I.V. dopamine was a slow rise in arterial pressure which reached a peak at least 5 s later than the hypoventilation. Similar pressor effects were potentiated or revealed in response to I.C. dopamine when sympathetic tone was inhibited with guanethidine, supporting the obvious conclusion that they were due to the direct vasoconstrictor effect of dopamine. O_2 also induced a slow rise in arterial pressure accompanied by peripheral vasoconstriction, both under pentobarbitone and Saffan. Since this was potentiated when sympathetic tone was inhibited with guanethidine and still occurred when ventilation was held constant, it cannot be ascribed to the action of sympathetic fibres or to secondary effects of the hypoventilation. Rather, it probably reflected the direct action of O_2 on vascular smooth muscle and/or the effect of a relative decrease in the concentration of vasodilator metabolites secondary to improved oxygenation of tissue cells. Accordingly, Honig, Frierson & Nelson (1971) reported that O_2 consumption of skeletal muscle of anaesthetized rats is transport-limited even at normal levels of arterial P_{O_2}.

However, the transient fall in arterial pressure which sometimes under pentobarbitone and consistently under Saffan, preceded both the pressor effect of O_2 and I.C. dopamine, occurred more or less simultaneously with the hypoventilation and was abolished by guanethidine. Therefore it can be ascribed to reflex inhibition of sympathetic activity resulting from unloading, respectively, one carotid body or all peripheral chemoreceptors (cf. Euler & Liljestrand, 1942). That the depressor response was enhanced by vagotomy is not surprising, because the inhibition of chemoreceptor discharge may then have been more complete, as argued above, and because the fall in arterial pressure would then have been buffered only by carotid baroreceptors and not by aortic baroreceptors. The depressor effect of O_2 after vagotomy should therefore give the most complete estimate of the effect of normoxic chemoreceptor drive on the cardiovascular system that can be made using the present techniques. In vagotomized rats under Saffan, arterial pressure commonly fell by 12–15 mmHg, i.e. by about 10% from resting levels, and simultaneously regional vascular resistance fell by approximately 10%. Thus, about 10% of total peripheral resistance can be attributed to normoxic chemoreceptor drive. Given the greater lability and smaller magnitude of O_2-induced depressor responses in rats under pentobarbitone, the contribution made by chemoreceptors to maintaining

arterial pressure was apparently less under that anaesthetic. This can be explained if it is accepted that chemoreceptor activity can readily activate the defence areas under Saffan, but not under pentobarbitone, for under Saffan the ventral medullary neurones of nucleus paragigantocellularis lateralis which seem to provide a major sympatho-excitatory drive for normal levels of arterial pressure, may receive a stronger excitatory drive via the chemoreceptor input to the defence areas as well as via a more direct input from nucleus tractus solitarius (see Marshall, 1986). The interesting question is whether the estimates made under Saffan give a good indication of the contribution made by normoxic chemoreceptor drive to the determination of arterial pressure in the conscious animal.

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