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RESPIRATORY EFFECTS OF SECTIONING THE CAROTID SINUS GLOSSOPHARYNGEAL AND ABDOMINAL VAGAL NERVES IN THE AWAKE RAT

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SUMMARY

1. Normoxic and hypoxic respiration has been measured in awake rats after denervation procedures designed to eliminate the regulatory input from the carotid bodies, from all chemosensory tissue supplied by the glossopharyngeal nerve (n. IX), and from abdominal chemoreceptors. Studies were made 1 day after section of the carotid sinus nerve (c.s.n.), n. IX (at a level including c.s.n.), the abdominal vagus (n. Xa) and combinations of these nerves. Results were compared with those found in normal controls.

2. C.s.n. section led to hypoventilation in both normoxia and hypoxia, reductions in respiratory frequency being consistent and substantial, and reductions in tidal volume varying with the degree of hypoxia.

3. By comparison, section of n. IX produced significantly greater reductions of both normoxic and hypoxic ventilation.

4. Section of n. Xa produced no significant change in normoxic ventilation but in hypoxia produced a significant small reduction in ventilation, mostly from an effect on tidal volume.

5. Denervation of all the associated chemosensory tissue by combined section of n. IX and n. Xa demonstrated a summation of effects but left two distinct residual responses, one to mild hypoxia, and one to severe hypoxia, both associated mainly with increases of tidal volume.

6. The experiments demonstrate that glomus tissues at different sites in the rat produce significant and distinct contributions to respiratory regulation. Denervation of all known receptors shows that significant ventilatory responses to hypoxia are still produced, either by unrevealed peripheral chemoreceptors, or by central neural mechanisms.

INTRODUCTION

Denervation of the carotid bodies is used regularly in respiratory experiments to modify or eliminate the input from peripheral chemoreceptors. The effect of denervation on respiratory control must depend on the extent to which the function of the carotid bodies can be replaced by that of other chemoreceptor tissue which has been described in the thorax and abdomen. Aortic bodies have been demonstrated

in dogs and cats (Coleridge, Coleridge & Howe, 1967, 1970) but not in rats (Barker, Easton & Howe, 1980). Their contribution to the ventilatory response to hypoxia immediately after carotid sinus nerve section is minimal in the cat (Miller & Tenney, 1975) and the pony (Bisgard, Forster & Klein, 1980), and non-existent in the rat (Sapru & Kreiger, 1977). Microscopic aggregations of tissue histologically resembling glomus tissue have been detected near the bifurcation of the innominate artery in rabbits (Palkama & Hopsu, 1965), as multiple small aggregations, 'miniglomera', around the carotid arteries of the cat (Matsuura, 1973), and along the course of the abdominal vagus nerve in the rat, mouse and hamster (Goormaghtigh, 1936; Hollinshead, 1941; Chen & Yates, 1970). From morphological and reflex evidence, Hollinshead (1946) suggested that these 'abdominal vagal paraganglia' were chemoreceptors functionally equivalent to the aortic bodies of other species. This hypothesis has been supported by electrophysiological evidence of chemoreceptor-like activity in sensory fibres of the abdominal vagus nerve (Andrews, Deane, Howe & Orbach, 1972; Howe, Pack & Wise, 1981).

We designed experiments to assess the relative physiological importance of the various chemoreceptor tissues. We sectioned the carotid sinus, glossopharyngeal and abdominal vagal nerves singly or in combination in the rat and 1 day later we studied respiration in the awake animal breathing air and hypoxic gases. The studies demonstrate a diversity of character and extent in the inputs from the various peripheral chemoreceptors and a summation of their effects, but show that their abolition leaves a residual respiratory response to hypoxia which may be central in origin.

METHODS

The rats used were females of the Charles Wistar strain, aged 93–104 days, weight 220–310 g, bred in specific-pathogen-free conditions. They were housed in animal laboratories, two or three to a cage, and provided with standard rat chow and water *ad libitum*.

Surgical procedures were carried out under halothane anaesthesia using a rodent anaesthetic machine (CIG Australia, Midget 3 Model). Anaesthesia was induced with 5% (v/v) halothane and maintained with 1–2% (v/v) halothane in oxygen flowing at 1–1·5 l min^{-1} to a rubber mask fitted loosely over the rat's mouth and nose. To denervate the carotid body, the carotid sinus nerve (c.s.n.) was located using the anatomical descriptions given by McDonald & Mitchell (1975) and Sapru & Kreiger (1977). The nerve was sectioned using iridectomy scissors and the two cut ends separated. The efficacy of carotid body denervation was established by demonstrating the abolition of ventilatory responses to brief hypoxia or to close arterial injection of NaCN (100 $\mu g\ kg^{-1}$) in preliminary experiments. Section of the glossopharyngeal nerve (n. IX) was performed by localizing the nerve and excising it 1–2 mm immediately proximal and distal to the origin of the carotid sinus nerve. In preparation for sectioning the abdominal vagus nerve (n. Xa), the animal was starved for 24 h to avoid gastric distension. A ventral mid-line incision was made caudally from the xiphisternum for 4–5 cm. The stomach and liver were retracted to allow access to the oesophagus. The dorsal and ventral vagi were located on the oesophageal surface, separated from connective tissue, and sectioned close to the diaphragm.

Ventilation was measured using a barometric plethysmograph in which the rat was held lightly restrained (Bartlett & Tenney, 1970). Rectal and ambient temperatures were continuously measured using thermistor probes. Relative humidity was measured using an artificial hair hygrometer. Changes in plethysmograph pressure due to ventilation were recorded on magnetic tape and analysed by a computer to produce measurements of tidal volume (V_T), respiratory frequency (f) and minute ventilation ($\dot{V}_E$), usually averaged over thirty breaths. V_T was calculated from the equation of Drorbaugh & Fenn (1955). Hypoxic mixtures were produced by combining air and nitrogen, and concentrations were checked with a paramagnetic oxygen analyser (Servomex

Control Ltd., Type OA101 Mk II) in samples taken from the level of the rat's head via tubing and a three-way tap in the Perspex lid of the plethysmograph. Test gases were passed through the plethysmograph at a flow rate of 5–7 l min^{-1}.

Respiratory tests were made 1 day (minimum 20 h) after anaesthesia. The rat was placed in the plethysmograph in an atmosphere of air for a preliminary period of 30 min, after which two respiratory recordings were made. Thereafter, 10 min were allowed between the introduction of each hypoxic gas mixture and respiratory measurements; the box was again flushed with the test gas for 2 min and the measurement repeated.

Studies were made on three groups, each of eight rats, 1 day after bilateral sectioning of c.s.n., n. IX or n. Xa. Immediately after the study, the animals with c.s.n. or n. IX section were subjected to bilateral subdiaphragmatic vagotomy. After a further interval of 1 day, they were retested. Measurements in all groups were compared with measurements made on twenty control rats of comparable age and weight.

Data analysis was performed by pooling all data within an experimental group and placing this data into bins according to the partial pressure of inspired oxygen (P_{I,O_2}) as follows: 40–50, 50–60, 60–70, 70–80, 80–90, 90–100, 100–110, 110–120, 120–130, and greater than 145 mmHg. An analysis of variance was performed for each bin using the six experimental groups. If the F statistic for the bin was significant, a protected t test was used on pairs of groups pre-selected on the basis of their interest. Thus, all statistics quoted represent the results of a protected t test. Tests were considered significant if P was less than 0·05.

RESULTS

Effects of single denervation procedures on ventilation in air

Bilateral c.s.n. section produced hypoventilation in air, both V_T and f being significantly lower than in controls. N. IX section similarly produced significantly lower V_T and f than in controls; $\dot{V}_E$ was also significantly lower than for c.s.n. section alone. Subdiaphragmatic vagotomy produced no significant difference from controls and produced no further reduction in $\dot{V}_E$ when undertaken following c.s.n. or n. IX section. Statistical details are given in Table 1.

TABLE 1. Comparison of tidal volume (V_T), respiratory frequency (f) and minute ventilation ($\dot{V}_E$) (mean ± S.E. of mean) in awake rats breathing air, after section of carotid sinus nerve (c.s.n.), glossopharyngeal nerve including c.s.n. (n. IX) abdominal vagus (n. Xa), and combinations of these nerves. Significant difference from controls: $*P < 0·05$, $**P < 0·01$, $***P < 0·001$; significant difference from c.s.n.: $\dagger P < 0·05$

	Control	C.s.n.	N. IX	N. Xa	C.s.n./ n. Xa	N. IX/ n. Xa
No. of observations...	34	16	16	16	14	15
V_T (ml)	2·05 ± 0·05	1·88 ± 0·05*	1·77 ± 0·06*	2·08 ± 0·07	1·92 ± 0·09	1·69 ± 0·05
f (min^{-1})	98 ± 3	85 ± 3*	75 ± 3*	90 ± 3	88 ± 6	78 ± 1
$\dot{V}_E$ (ml min^{-1})	198 ± 6	159 ± 7***	133 ± 6***†	185 ± 6	170 ± 16	133 ± 6

Effects of single denervation procedures on hypoxic respiration

Control animals showed no great change of f as P_{I,O_2} was lowered to 105 mmHg, a progressive increase of f at P_{I,O_2} below 105 mmHg and two distinct increases of V_T at P_{I,O_2} 127 and 55 mmHg. Consequently, $\dot{V}_E$ showed progressive increases with the degree of hypoxia.

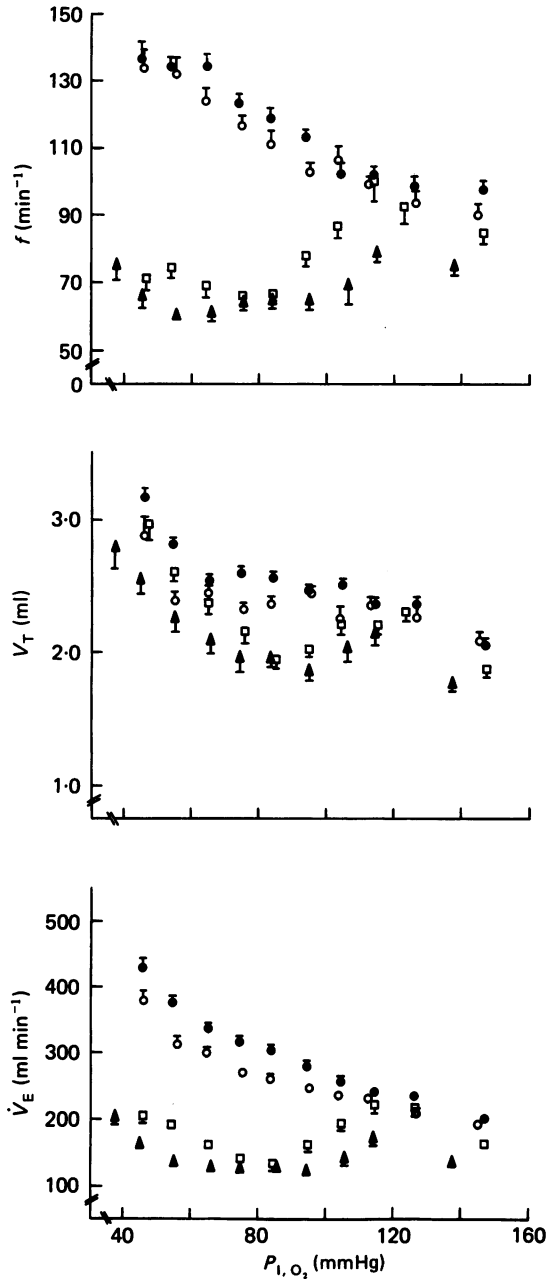

Fig. 1. Comparison of respiratory frequency (f), tidal volume (V_T) and minute volume ($\dot{V}_E$) at different levels of inspired oxygen (P_{I,O_2}) in intact control rats (●) (mean and S.E. of mean) and awake rats 1 day after bilateral section of the abdominal vagus nerves (n. Xa; ○), the carotid sinus nerves (c.s.n.; □) or the glossopharyngeal nerves at a level including c.s.n. (n. IX; ▲).

The comparison between controls and c.s.n.-sectioned rats is shown in Fig. 1. After bilateral c.s.n. section, f was significantly lower than that of controls ($P < 0{\cdot}01$ to $< 0{\cdot}001$) at all P_{I,O_2} levels except 115 mmHg; and only in the P_{I,O_2} range 127–115 mmHg did f rise above the air-breathing values. The V_T response was significantly depressed compared with controls between P_{I,O_2} 105 and 75 mmHg but not outside this range. $\dot{V}_E$ increased above air values at P_{I,O_2} 127–105 mmHg, but was below the air value at P_{I,O_2} 95 mmHg, this depression being highly significant compared with controls; and in severe hypoxia $\dot{V}_E$ increased but remained significantly below control levels.

Respiratory patterns in all rats 1 day after bilateral section of n. IX were similar to those following c.s.n. section, but the changes were greater. V_T, f and $\dot{V}_E$ were all reduced over the whole range of P_{I,O_2} and differences from control were highly significant (for f and $\dot{V}_E$, $P < 0{\cdot}001$; for V_T, $P < 0{\cdot}05$ to $< 0{\cdot}001$). The results are illustrated in Fig. 1.

Direct comparison of the effects of c.s.n. and n. IX sections (Fig. 1) shows the generally more-depressed respiratory response after n. IX section. Statistically significant differences occurred in f and $\dot{V}_E$ values at P_{I,O_2} 127–95 mmHg ($P < 0{\cdot}05$ to $< 0{\cdot}001$).

All rats, 1 day after bilateral subdiaphragmatic vagotomy, showed smaller V_T and f responses than controls at all levels of P_{I,O_2} except 105 mmHg. Differences for V_T were statistically significant ($P < 0{\cdot}05$) at four of seven P_{I,O_2} levels below 115 mmHg; f was not consistently modified. As a result, $\dot{V}_E$ was significantly below control levels at eight of ten levels of P_{I,O_2} ($P < 0{\cdot}05$ to $< 0{\cdot}001$). Results are shown in Fig. 1.

Effects on hypoxic respiration of subdiaphragmatic vagotomy following c.s.n. or n. IX section

In eight rats studied after combined section of c.s.n. and n. Xa, the hypoxic frequency response was consistently less than after c.s.n. section, and V_T was reduced at a P_{I,O_2} below 85 mmHg. Consequently, $\dot{V}_E$ was consistently reduced at P_{I,O_2} below 85 mmHg (Fig. 2*A*).

In eight rats studied after combined section of n. IX and n. Xa, f was less than after n. IX section at P_{I,O_2} below 85 mmHg, V_T was less than after n. IX section at all levels of hypoxia, and $\dot{V}_E$ was reduced at P_{I,O_2} less than 105 mmHg (Fig. 2*B*). These differences were, however, small and not statistically significant at any single level of P_{I,O_2}.

Even after the most extensive denervation, combined section of n. IX and n. Xa (Fig. 2*B*), there was a consistent V_T response to hypoxia at P_{I,O_2} below 85 mmHg. This resulted in a significant residual ventilatory response to severe hypoxia despite the denervation procedures.

DISCUSSION

The experiments demonstrated a depression of normoxic and hypoxic respiration following denervation of the carotid bodies; a respiratory role in air and hypoxia for tissue other than the carotid body supplied by n. IX; and a significant role of abdominal chemoreceptors in hypoxic conditions.

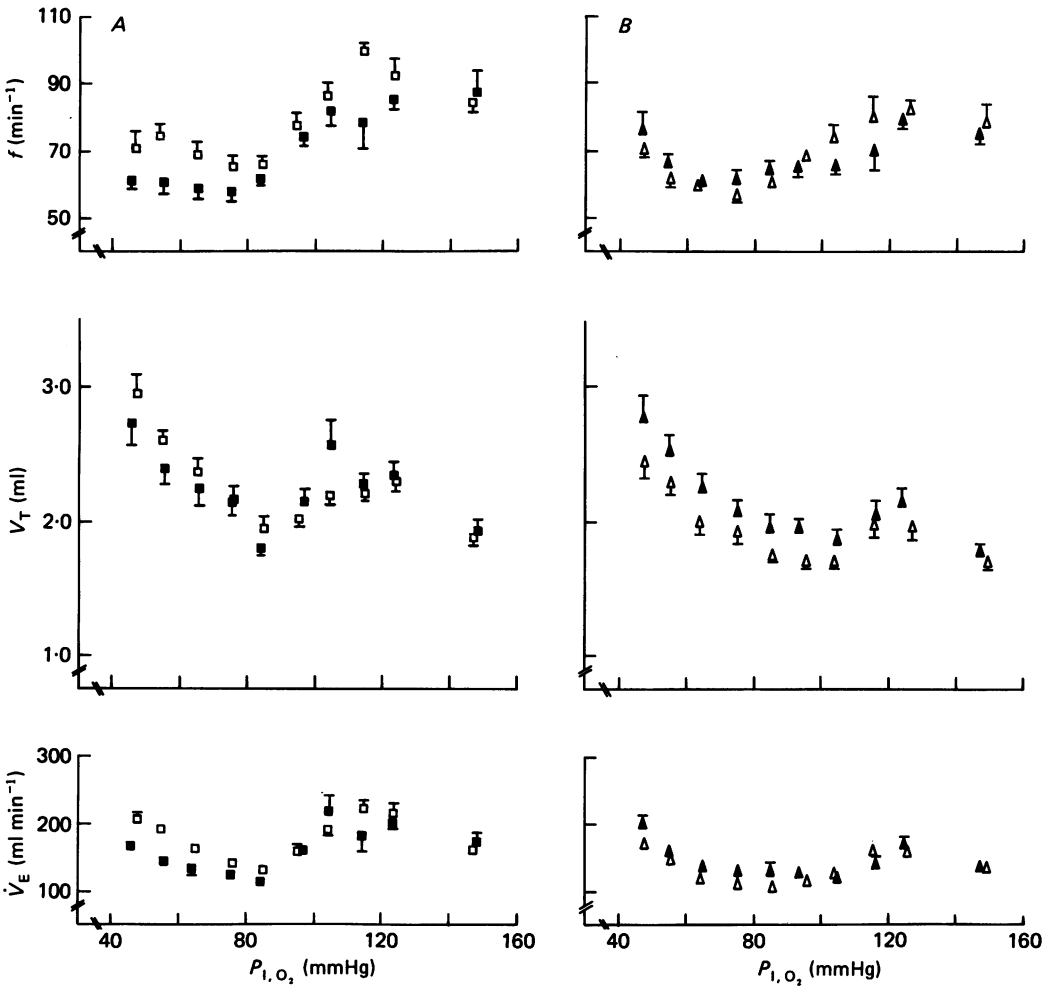

Fig. 2. Levels of f, V_T and $\dot{V}_E$: *A*, after combined section of c.s.n. and n. Xa (■) compared with c.s.n. alone (□); *B*, after combined section of n. IX and n. Xa (△) compared with n. IX alone (▲).

In studying patterns after denervation procedures, it should be emphasized that the experiments do not demonstrate the total contribution previously made by the denervated tissue. As some functions may be replaced by inputs from other chemosensory tissues, the normal contribution may be greater than that which is lost after denervation.

Ideally respiratory patterns in hypoxia should be related to changes of arterial P_{O_2}, but the number of measurements required for repeated studies in small animals makes such arterial sampling impossible. Data obtained in our laboratory and elsewhere would allow P_{I,O_2} values to be presented in terms of predicted arterial P_{O_2} values but we prefer to use measured values.

The role of the carotid bodies

The experiments confirmed that the carotid bodies produce a significant stimulus to respiration in the awake animal breathing air, so that denervation leads to hypoventilation. This observation confirms those made in rats (Favier & Laccaisse, 1978; Cardenas & Zapata, 1983), dogs (Bouverot, Candas & Libert, 1973), cats (Gautier & Bonora, 1979), goats (Bisgard, Forster, Klein, Manohar & Bullard, 1980), rabbits (Chalmers, Korner & White, 1967), calves (Bisgard & Vogel, 1971) and ponies (Bisgard, Forster, Orr, Buss, Rawlings & Rasmussen, 1976). In hypoxia, denervation of the carotid bodies produces a striking depression of respiration.

The role of chemosensory tissues other than carotid bodies

The further depression of normoxic and hypoxic respiration produced by n. IX section following c.s.n. section cannot be attributed to the trivial motor function of n. IX (to the stylopharyngeus muscle), and therefore is evidence for chemoreceptor tissue in the cervical region additional to the carotid bodies. Miniglomera described in this area in the rabbit (Matsuura, 1973) are not innervated by the carotid sinus nerve. Existence of comparable tissue in the rat can now be assumed. Its functional role is significant and will have been attributed to the carotid bodies when their denervation has been effected by n. IX section (Cragg, Drysdale & Singh, 1981; Cardenas & Zapata, 1983).

The insignificant effects of subdiaphragmatic vagotomy on respiration in air suggested that abdominal chemoreceptors made no unique contribution to normoxic respiration. A physiological role of these receptors was demonstrated, however, in hypoxia and was further supported by the increased depression of respiratory response to hypoxia seen in rats with c.s.n. or n. IX section subjected to abdominal vagotomy. Since all effects were seen only in hypoxia and not in normoxic respiration, they cannot readily be attributed to ventilatory effects of the abdominal surgery associated with vagal section. Studies on rats subjected to sham vagal section showed no effect of the procedure.

The summation of peripheral chemoreceptor inputs

The effects of the three denervation procedures in the present work lead us to hypothesize that various chemoreceptor tissue aggregations contribute to the total chemoreceptor input to the C.N.S., but each has a maximum sensitivity at a different level of hypoxia. The carotid bodies, as expected, contribute the major input and particularly affect V_T in moderate hypoxia and f in mild and severe hypoxia. Other chemoreceptors served by n. IX, whose existence has been previously unknown in the rat, play an important part in controlling f in mild to moderate hypoxia but have little effect on V_T. Abdominal chemoreceptors mostly affect V_T in moderate and severe hypoxia. Thus, we postulate that the total chemosensory input to the C.N.S. in hypoxia is a summation of inputs from different chemoreceptor sites, some anatomically identified and others of unknown location.

Hypoxic respiration following peripheral chemodenervation

Following the substantial denervation of peripheral chemoreceptors achieved by combined section of n. IX and n. Xa, the respiratory patterns of our awake rats during exposure to severe hypoxia showed two major characteristics: a depression of f at P_{I,O_2} below 95 mmHg and an increase of V_T and $\dot{V}_E$ at P_{I,O_2} below 85 mmHg.

Previous studies of the effects of carotid body denervation are not generally comparable. In rats, the carotid bodies have been subjected to trauma without identification of the carotid sinus nerves (Maskrey, Megirian & Nicol, 1981), and these and other studies (Favier & Lacaisse, 1978) have been made without reference to the interval required for recovery of responses (Bisgard *et al.* 1976). The tachypnoea seen after carotid body denervation in the cat (Miller & Tenney, 1975) is associated with alterations in suprapontine monoamine metabolism (Gautier & Bonora, 1980) which do not occur in the rat (Davis & Carlsson, 1973). The tachypnoea of the cat may be a characteristic of species which pant; the rat does not (Hart, 1971). Further species differences were demonstrated by Bouverot *et al.* (1973). In other studies there are major variations of technique, including uncertainty as to aortic body input in partially denervated animals (Tenney & Brooks, 1966), the extent of hypoxic exposure (Chalmers *et al.* 1967), the duration of exposure (Davenport, Brewer, Chambers & Goldschmidt, 1947) and the use of anaesthesia (Bouckaert, Heymans & Samaan, 1938; Moyer & Beecher, 1942).

We considered whether our results might have been produced by cumulative hypoxia but a random sequence of tests excluded this possibility: single 10–15 min exposures to severe hypoxia also produced the characteristic responses demonstrated in Figs. 1–2.

The possibility that the residual response of V_T might arise from peripheral chemoreceptor tissue not denervated by section of n. IX and n. Xa cannot be totally excluded. Potential chemoreceptor sources include the aortic bodies and other thoracic 'miniglomera' (Matsuura, 1973), neuroepithelial bodies in the lungs (Lauweryns & Cokelaere, 1973), and abdominal tissue supplied by the splanchnic nerve (Hollinshead, 1946). A significant residual contribution from aortic bodies is improbable. Histologically, such tissue has been found to be trivial or non-existent in the rat (Hollinshead, 1946; Barker *et al.* 1980). Recordings from the aortic nerves of the rat show activity characteristic of baroreceptor input only, and there is no response to appropriate respiratory stimulants injected into the ascending aorta (Sapru & Kreiger, 1977). These authors showed that respiratory stimulation following the injections was abolished by section of the c.s.n. Unpublished studies in our laboratory have shown no alteration of the ventilatory response to hypoxia following bilateral aortic nerve section in the rat. Awake rats with nearly total elimination of vagal input have been prepared in our laboratory (Body, 1984) but we have been unable to produce survivors in animals with preceding section of n. IX.

Generally, residual effects after denervation have been regarded as central in origin, a balance between the depressive effect on respiratory neurones of hypoxia and hypocapnia and a stimulatory effect of the associated metabolic disturbances, including reduced cerebrospinal fluid HCO_3^- (Cherniack, Edelman & Lahiri, 1970; Bouverot *et al.* 1973; Lee & Milhorn, 1975; Dempsey & Forster, 1982). Stimulation

has been observed in denervated dogs (Krasney, Magno, Levitzky, Koehler & Davies, 1973), goats (Bisgard *et al.* 1980), calves (Bisgard & Vogel, 1971), cats (Miller & Tenney, 1975) and rabbits (Bouverot *et al.* 1973).

The production of brain hypoxia by reduction of blood flow has been shown to stimulate ventilation in moderate and severe hypoxia in awake goats (Chapman, Santiago & Edelman, 1979). The reversal of stimulation produced by anaesthesia (Moyer & Beecher, 1942; Miller & Tenney, 1975) may explain the depression observed in rats by Cragg *et al.* (1981).

Studies in the fetal lamb reviewed by Dawes (1984) show results interestingly comparable with ours. In the fetus near term, hypoxia decreases or abolishes breathing movements; the carotid bodies are functional, but their effects are inhibited by a mechanism apparently located near the hypothalamus; and transection of the brain reveals a residual stimulatory action of hypoxia. It is tempting to consider that at least in the rat, but possibly in other mammals if experiments were appropriately designed, central respiratory responses to hypoxia in the awake state represent the sum of multiple stimulatory and depressing effects, including a specific but as yet unlocated mechanism depressing frequency and a more general mechanism enhancing tidal volume.

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