ROLE OF PERIPHERAL CHEMORECEPTORS AND CENTRAL CHEMOSENSITIVITY IN THE REGULATION OF RESPIRATION AND CIRCULATION

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SUMMARY

Adjustments of respiration and circulation in response to alterations in the levels of oxygen, carbon dioxide and hydrogen ions in the body fluids are mediated by two distinct chemoreceptive elements, situated peripherally and centrally. The peripheral arterial chemoreceptors, located in the carotid and aortic bodies, are supplied with sensory fibres coursing in the sinus and aortic nerves, and also receive sympathetic and parasympathetic motor innervations. The carotid receptors, and some aortic receptors, are essential for the immediate ventilatory and arterial pressure increases during acute hypoxic hypoxaemia, and also make an important contribution to respiratory compensation for acute disturbances of acid-base balance. The vascular effects of peripheral chemoreceptor stimulation include coronary vasodilation and vasoconstriction in skeletal muscle and the splanchnic area. The bradycardia and peripheral vasoconstriction during carotid chemoreceptor stimulation can be lessened or reversed by effects arising from a concurrent hyperpnoea.

Central chemoreceptive elements respond to changes in the hydrogen ion concentration in the interstitial fluid in the brain, and are chiefly responsible for ventilatory and circulatory adjustments during hypercapnia and chronic disturbances of acid-base balance. The proposal that the neurones responsible for central chemoreception are located superficially in the ventrolateral portion of the medulla oblongata is not universally accepted, mainly because of a lack of convincing morphological and electrophysiological evidence. Central chemosensitive structures can modify peripheral chemoreceptor responses by altering discharges in parasympathetic and sympathetic nerves supplying these receptors, and such modifications could be a factor contributing to ventilatory unresponsiveness in mild hypoxia. Conversely, peripheral chemoreceptor drive can modulate central chemosensitivity during hypercapnia.

INTRODUCTION

During various physiological states that alter metabolic activity in the body, the goal of ventilation is to maintain proper concentrations of oxygen, carbon dioxide and hydrogen ions in the body fluids. The summated metabolic activity of individual cells is thus the ultimate factor regulating respiratory activity.

For many years it was thought that the hyperventilatory changes associated with hypoxia and hypercapnia resulted from direct stimulation of elements located within the so-called respiratory centres in the brain. A revision of this view became necessary following the discovery of the chemoreceptor function of the carotid and aortic bodies, and the description of the ultimate responsibility of these peripheral receptors for the immediate increase in breathing produced by oxygen lack (Heymans & Heymans, 1927; Heymans & Bouckaert, 1930). Although peripheral chemoreceptors were shown to be capable of mediating an increase of ventilation in hypercapnic conditions, it was also found that respiratory stimulation in this condition could still be elicited in animals deprived of the peripheral chemoreceptor input to the brain. This finding indicated that chemical regulation of respiration involved both central and peripheral chemosensitivity.

An impetus to the study of central chemosensitivity was provided by the pioneering work of Leusen (1954a, b), who developed ventricular perfusion techniques, and showed that a reduction in the pH of the artificial cerebrospinal fluid perfusing the ventricles caused ventilation to increase. More recent investigations, mainly carried out by Loeschcke and his associates, have presented evidence that structures sensitive to changes in pH and carbon dioxide are located in the superficial surfaces of the ventrolateral portion of the medulla oblongata (see Loeschcke, 1965). These central chemosensitive structures have been shown to be important in the control of both respiration and circulation in hypercapnic conditions.

The current view of the chemical control of respiration, as illustrated in Fig. 1, envisages the existence of two separate chemosensitive areas with different stimulus-response characteristics. However, these two chemoreceptive areas do not act independently of each other and, therefore, cannot be viewed in isolation. Thus, there is evidence that central chemosensitive structures can modify by neural pathways the peripheral chemoreceptors and visa versa.

The purpose of this article is not to review in any great detail either the morphology or receptor mechanisms of peripheral and central chemosensitive elements but rather to emphasise the importance of an interplay of these structures in the chemical regulation of respiration and to a lesser extent of circulation.

PERIPHERAL ARTERIAL CHEMORECEPTORS

The peripheral arterial chemoreceptors of major importance in the reflex control of respiration and circulation are located in the carotid and aortic bodies (see Heymans & Neil, 1958). The carotid bodies, situated at the carotid bifurcations, are supplied with sensory nerve fibres which course in the sinus nerves, branches of the glossopharyngeal. Additionally, each organ receives both a sympathetic and parasympathetic (sinus
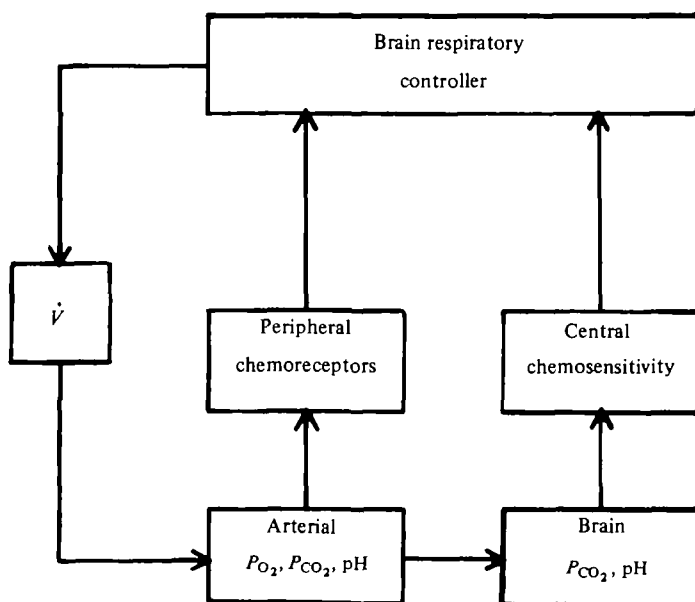
Fig. 1. Diagram illustrating the chemosensitive elements responsible for mediating ventilatory adjustments in response to changes of P_{O_2}, P_{CO_2} and pH in the body fluids, $\dot{V}$, ventilation.

nerve efferents) motor innervation (see O'Regan, 1977). The aortic bodies, located in the region of the aortic arch and the roots of the major arteries in the thorax, are innervated by efferent and afferent fibres coursing in the aortic nerves, branches of the vagus, and these organs are also supplied with sympathetic efferent fibres.

The peripheral chemoreceptors have a complex morphology (see Verna, 1979). Briefly, the functional unit of chemoreception would appear to be a cluster of cells of two types, each cluster receiving an innervation from one or at most two sensory axons of chemosensory nerves. The most numerous of the cells (type 1) have dense-cored vesicles in their cytoplasm, contain catecholamines (dopamine and noradrenaline) and make extensive synaptic contacts with sensory axons, although it appears that some of these cells are not innervated. Synaptic contacts between adjoining type I cells also occur. The cluster of type I cells, surrounded by the thin type II cells and an extensive capillary network, may also receive an autonomic nerve supply (see O'Regan, 1977, 1981).

Stimulus-response relations

Because of its larger size, its easier accessibility and vascular isolation together with a minimal disturbance to respiration during experimentation, the carotid body has been the organ of choice for the study of peripheral chemoreceptor responses to a variety of stimuli. However, it is now apparent that the carotid and aortic receptors differ, not only in the characteristics of their responses to various stimuli, but also in the reflex effects they engender when activated.

Peripheral chemoreceptor responses have mainly been assessed by monitoring action potentials in chemosensory preparations obtained from cut sinus and aortic

nerves in the cat. Whole nerve, multi-fibre, few-fibre and single fibre preparations have been used. Responses to the four classical types of hypoxia and to hypercapnia and acidaemia have been extensively investigated for more than four decades. There is a reasonable consensus of opinion concerning these responses although some problems still remain.

Peripheral chemoreceptor responses to changes in oxygen tension, carbon dioxide tension and pH in the arterial blood: Investigations involving the recording of activity from single chemosensory units of the sinus nerve (Biscoe, Purves & Sampson, 1970; Lahiri & DeLaney, 1975 a, b) demonstrated stimulus-response relations during steady-state changes in arterial oxygen tension (P_{a, O_2}), arterial carbon dioxide tension (P_{a, CO_2}) and arterial pH (pHa) which were in general agreement with other studies employing whole nerve or multi-fibre preparations (see Torrance, 1968; Biscoe, 1971). In isocapnic conditions responses during changes in P_{a, O_2} display a hyperbolic pattern. Small reductions in impulse frequency occur as P_{a, O_2} is increased from normoxia (P_{a, O_2}, 90–110 torr.) to hyperoxia (P_{a, O_2}, > 400 torr.). As P_{a, O_2} is reduced below normoxic levels, impulse frequency increases markedly although there may be an inhibition of discharge in severe hypoxia (P_{a, O_2} < 20 torr.). In circumstances where levels of P_{a, O_2} are maintained constant, the discharge frequency of single chemosensory units increases linearly as P_{a, CO_2} is elevated in the range 20–60 torr. With values of P_{a, CO_2} between 10 and 15 torr., depending on the level of P_{a, O_2}, chemosensory activity is abolished or at least discharges are very infrequent. There is also a linear elevation in chemosensory discharge frequency as H^+ concentration is increased in range 20–60 nM. An important feature of carotid chemoreceptor responses is that when hypoxic and hypercapnic stimuli are combined, a multiplicative interaction occurs (see later). Carotid chemosensory units appear to form a homogeneous group in their response patterns to changes in P_{a, O_2} and P_{a, CO_2}, although the mean level of discharge at any given level of stimulus varies greatly between individual fibres.

Following the hypothesis of Yamamoto (1960) that variations in P_{a, CO_2} with time could provide a stimulus to respiration different from steady levels of P_{a, CO_2}, it was reported by Black, McCloskey & Torrance (1971) that carotid chemoreceptors showed adaptation to step changes in P_{CO_2}. Oscillations in pHa due to respiratory induced variations of P_{a, CO_2} are normally present (Band, Cameron & Semple, 1969) and provide a stimulus to the carotid chemoreceptors that is dynamic rather than steady. Oscillations in sinus nerve chemosensory discharges with the same period as respiration have been described (Biscoe & Purves, 1967; Goodman, Nail & Torrance, 1974), indicating a role in respiratory control for dynamic changes in P_{a, CO_2} (see later).

The more limited studies carried out on aortic chemoreceptors indicate that these receptors are considerably less responsive to changes in P_{a, O_2}, P_{a, CO_2} and pHa than are the carotid chemoreceptors. The lack of or lessening of hypercapnic responses, initially reported by Paintal & Riley (1966), has been attributed to a rapid adaptation of aortic chemoreceptors to changes in P_{a, CO_2} (Hanson, Rao & Torrance, 1979). Thus, these receptors respond transiently to hypercapnic stimuli but this response is not maintained under steady-state conditions.

Peripheral chemoreceptor responses to stagnant hypoxia: Landgren & Neil (1951) found that hypotension, induced by bleeding in artificially ventilated cats, markedly in-

creased the discharge rate of multi-fibre chemosensory units of the sinus nerve. Sub-
sequent studies showed that the rate of venous outflow (total blood flow) of the
carotid body was reduced during hypotension, emphasising the role of stagnation in
the genesis of the enhanced chemosensory discharges (Daly, Lambertsen & Schweitzer,
1954). Although Lee, Mayou & Torrance (1964) confirmed the findings of Landgren &
Neil using chemosensory afferents prepared from the aortic nerve, other studies
disagreed that carotid chemoreceptors are affected by changes in arterial pressure. It
was shown that the activity recorded from single chemosensory units of the sinus
nerve was unaffected in the steady-state by changes in arterial pressure in the range
70–160 torr., although transient alterations in impulse frequency could occur (Biscoe,
Bradley & Purves, 1970; Lahiri *et al.* 1980). Indeed, hypotension down to a level of
50 torr. only slightly affected carotid chemoreceptor discharges (Lahiri *et al.* 1980).
Autoregulation of carotid body total flow has been reported, a circumstance greatly
influenced by the levels of P_{a, CO_2} and the anaesthetic used (McCloskey & Torrance,
1971). Of more importance in this context are the findings of Acker, Lübbers & Durst,
(1977) that local flow, monitored by electrodes inserted into the carotid body, is
unaffected in the steady-state by changes of arterial pressure, although alterations of
the total blood flow of the organ does occur. The balance of evidence, therefore,
favours the view that carotid chemoreceptors are insensitive to steady-state changes
in arterial pressure over a wide range. However, carotid chemosensory units may not
form a homogeneous group in their responses to pressure changes. It has been re-
ported that steady-state hypotensive changes can leave chemosensory discharges of
different units unchanged, increased or even depressed (Mitchell & McCloskey, 1974;
Majcherczyk *et al.* 1980). Unlike carotid chemoreceptors, it appears that aortic
chemosensory units are highly sensitive to arterial pressure changes (Lee *et al.* 1964;
Lahiri *et al.* 1980).

Peripheral chemoreceptor responses to anaemic hypoxia: Study of the effects of
carboxyhaemoglobinaemia (HbCO) on sinus and aortic nerve chemosensory discharges
has been the method usually employed to evaluate the responses of peripheral chemo-
receptors to anaemic hypoxia. Duke, Green & Neil (1952) reported that 75 % HbCO
during normoxia did not excite carotid chemosensory activity, a finding that has
received support in subsequent studies (see Fitzgerald & Traystman, 1980; Lahiri *et al.*
1981). Although some disagreement does exist (Mills & Edwards, 1968), this could be
explained by a lack of homogeneity of carotid chemosensory units. Thus, a small
number of units do increase their activity during moderate HbCO (Lahiri *et al.* 1981).
On the other hand, most aortic chemosensory units have been shown to respond to
moderate HbCO (Paintal, 1967; Lahiri *et al.* 1981). Studies of the effects of graded
anaemia induced by dextran-for-blood exchange confirm the results obtained during
HbCO, in that carotid chemoreceptors are little affected until anaemia is severe
(haematocrit < 15), whereas aortic chemoreceptors are readily stimulated by mode-
rate reductions in haematocrit (Hatcher, Chiu & Jennings, 1978).

Peripheral chemoreceptor responses to histotoxic hypoxia: Extensive investigations
have shown that peripheral chemoreceptors are markedly excited by histotoxic
hypoxia induced by poisons that interfere either with electron transfer along the intra-
cellular respiratory chain or with the various enzyme systems associated with this

chain-glycolysis and the Krebs cycle (see Heymans & Neil, 1958; Anichkov & Belen'kii, 1963). In addition, agents that uncouple oxidative phosphorylation also enhance peripheral chemoreceptor activity.

Efferent influences on peripheral chemoreceptor responses: The stimulus-response relations described above were mainly determined using chemosensory preparations obtained from cut sinus and aortic nerves, circumstances which of necessity eliminated from consideration any influences exerted on the receptors by parasympathetic efferent fibres coursing in these nerves. It is known that activation of sinus nerve efferent fibres can suppress peripheral chemosensory activity, and also increase carotid body blood flow (Neil & O'Regan, 1971 a). Because many of the stimuli known to affect carotid chemoreceptor activity also alter discharges in parasympathetic efferent fibres in the sinus nerve (see O'Regan, 1977; Majcherczyk *et al.* 1980), it cannot be assumed that stimulus-response relations derived from cut nerves are essentially the same as those that would be obtained if the nerves were intact (see later).

Consideration needs also to be given to a role for sympathetic nerves in modulating peripheral chemosensory activity. Activation of the sympathetic supply to the carotid body causes excitation of chemosensory activity (Floyd & Neil, 1952) and reduces carotid body blood flow (Daly *et al.* 1954). Excitatory responses of chemosensory activity appear to depend on vascular and non-vascular mechanisms (Acker & O'Regan, 1981; O'Regan, 1981) and there is also evidence that sympathetic efferent fibres can inhibit chemoreceptor activity (O'Regan, 1981). It is well known that sympathetic discharges increase during peripheral chemoreceptor stimulation, and this elevated sympathetic activity could in turn modulate the chemoreceptors. Investigation of stimulus-response relations of peripheral chemoreceptors have largely ignored the role of sympathetic nerves. These nerves were either sacrificed during experimentation or, if intact, their role was not adequately evaluated.

Peripheral chemoreceptor reflex effects

In the 20 years or so following the discovery of the chemoreceptor function of the carotid and aortic bodies, it was found that these chemoreceptors mediate major reflex effects on respiration and circulation (see Heymans & Neil, 1958). These effects have now been analyzed in greater detail, using both anaesthetized and unanaesthetized animals, some of which were acutely or chronically deprived of their peripheral chemoreceptor function. Attempts have been made to establish as precisely as possible the role of these receptors in respiratory and circulatory control during normal and abnormal states. Of some importance in this context are the investigations carried out on human subjects who have had their carotid bodies resected (CBR) for the treatment of asthma and other obstructive diseases of the airways (see Whipp & Wasserman, 1980).

Peripheral chemoreceptor reflex effects on ventilation: It is well established that the hyperpnoeic and hypertensive responses during acute episodes of hypoxic hypoxaemia are entirely dependent on the integrity of peripheral chemoreceptors and their reflex pathways (see Heymans & Neil, 1958). Thus, in anaesthetized animals with de-nervated peripheral chemoreceptors, severe hypoxia, induced by breathing 5–10% oxygen, leads to apnoea and hypotension instead of the usual responses. While such

profound effects are not seen during less severe hypoxia in conscious animals deprived of their peripheral chemoreceptor function, these hypoxic animals do not exhibit the typical pattern of ventilatory responses to acute hypoxia, although there may be a tachypnoea with a reduced tidal volume (see Mitchell, 1965). It is also evident that carotid chemoreceptors mediate all or much the greater proportion of the ventilatory response to acute hypoxia, and this has been shown to be so in all species of animal studied so far. Indeed, steady-state and transient reductions in P_{a,O_2} levels, sufficient to increase ventilation and arterial pressure in normal individuals, are without effect or may cause hypoventilation and hypotension in CBR subjects (see Whipp & Wassermann, 1980). A small recovery of ventilatory responses to hypoxia occurring months or years after removal of the carotid bodies has been described in humans and other animals, a circumstance that has been ascribed to an increased sensitivity of previously dormant aortic bodies (Smith & Mills, 1980).

Peripheral chemoreceptors, almost exclusively those present in the carotid bodies, contribute a small proportion to the steady-state ventilatory response to hypercapnia, the magnitude of which depends on the prevailing level of P_{a,O_2} (see Whipp & Wasserman, 1980). Based on studies carried out on CBR subjects, it has been estimated that in normoxia between 20 and 30% of the ventilatory response during hypercapnia is mediated by carotid chemoreceptors. During hyperoxia the contribution by these receptors is negligible but becomes more marked as P_{a,O_2} is reduced below normoxic levels, this latter effect being a reflection of multiplicative interaction of hypoxia and hypercapnia within the carotid body. A smaller or no contribution by carotid chemoreceptors to steady-state ventilatory responses during hypercapnia has been reported in other animal species (see Mitchell, 1965; Pappenheimer, 1967).

A more significant contribution to ventilation by carotid chemoreceptors may be present when hypercapnic stimuli are dynamic rather than steady. The effects of dynamic hypercapnic stimuli on ventilation depend on whether the stimuli are presented to the carotid body in inspiration or expiration (Black & Torrance, 1971). The significance of dynamic stimuli in ventilatory control, especially in exercise, is still a subject of controversy (see Cunningham, 1974; Whipp & Davis, 1979).

The important contribution made by carotid chemoreceptors to the hyperventilation in acute metabolic acidosis appears to be now well established (see Mitchell, 1965; Whipp & Davis, 1979). However, such a view is not universally accepted (see Pappenheimer, 1967), possibly indicating that there may exist a species difference in the relative contribution of central and peripheral chemosensitive elements to ventilatory compensation for this condition. The slowness of exchange of H^+ and HCO_3^- across the blood–brain barrier puts carotid chemoreceptors in an advantageous position to counteract acute disturbances of acid-base balance but the relative contribution by these receptors in chronic situations may be much less marked.

Provided hypotension is marked, stagnant hypoxia can sufficiently stimulate carotid chemoreceptors to cause hyperventilation (Landgren & Neil, 1951). On the other hand, the lack of ventilatory changes in anaemic hypoxia (Bartlett & Tenney, 1970) reflects the unresponsiveness of carotid chemoreceptors in this condition. As aortic chemoreceptors do respond during moderate anaemia, it illustrates once more the minor role mediated by these receptors in ventilatory control.

Peripheral chemoreceptor reflex effects on circulation: Peripheral chemoreceptors, although they exert little influence on the cardiovascular system in normal circumstances, become important in helping to maintain arterial pressure and to redistribute blood flow during acute episodes of hypoxic hypoxia, stagnant hypoxia, asphyxia and metabolic acid-base disorders. In some abnormal states effects reflexly exerted by peripheral chemoreceptors on the heart and blood vessels can be of crucial importance in counteracting depressant influences on the cardiovascular system arising either from concurrent activation of other afferent fibres or from central and peripheral changes induced by the very stimuli responsible for the chemoreceptor excitation.

It is well established that the elevation in arterial pressure consequent on peripheral chemoreceptor excitation is predominantly due to an increase in total peripheral resistance but the contribution by different vascular beds to this peripheral vasoconstriction is variable. Although there may be some disagreement concerning the magnitude of changes, there is little doubt that during peripheral chemoreceptor stimulation vasoconstriction occurs in skeletal muscle, intestine and kidney (see Heistad & Abboud, 1980; Vatner & Rutherford, 1981). Both vasodilation (Calvedo *et al.* 1970) and vasoconstriction (Daly & Scott, 1962; Little & Öberg, 1975) of skin blood vessels have been reported to occur during carotid chemoreceptor activation but the type of responses obtained in this circulation seems to depend on the level of sympathetic tone prevailing at the time of measurement and on whether flow in nutritional or shunt vessels is being recorded (Little & Öberg, 1975).

In contrast to the vasoconstrictor effects described above, the coronary circulation undergoes a vasodilation in response to carotid chemoreceptor excitation, an effect which depends in part on an activation of vagal cholinergic vasodilator fibres (see Heistad & Abboud, 1980; Vatner & Rutherford, 1981). The cerebral circulation also dilates in response to many of the stimuli known to excite peripheral chemoreceptors but the role of these receptors in the genesis of this response is highly controversial (see Heistad & Marcus, 1978; Purves, 1978; Fitzgerald & Traystman, 1980).

The finding, reported by Daly & Scott (1958), that carotid chemoreceptor stimulation induces a bradycardia in dogs with controlled ventilation, has been amply confirmed to be the primary reflex effect on heart rate mediated by these receptors, and this has been shown to be so in a wide variety of animal species. Less certain are the inotropic effects of carotid chemoreceptor stimulation; decreases, increases or no changes in cardiac contractility have been reported to occur (see Vatner & Rutherford, 1981). The reflex cardiac effects mediated by aortic chemoreceptors appear to differ from those due to carotid chemoreceptor activation, in that most studies support the initial findings of Comroe & Mortimer (1964) that stimulation of these receptors induce tachycardia and positive inotropic effects rather than bradycardia and variable effects on contractility.

The primary reflex effects on the heart and blood vessels due to carotid chemoreceptor stimulation can be antagonized or potentiated by influences occurring simultaneously. Thus, the hyperventilation accompanying carotid chemoreceptor activation leads to an increase in vagal afferent activity from pulmonary stretch receptors, and this increased activity can, possibly, in association with hypocapnia and enhanced activity of respiratory neurones in the medulla, produce a reduction or even

a reversal of the chemoreceptor mediated hypertension, peripheral vasoconstriction and bradycardia (Daly & Scott, 1958, 1962; Vatner & Rutherford, 1981). Conversely, primary influences due to carotid chemoreceptor stimulation are considerably enhanced during apnoeic episodes induced either by excitation of upper airway receptors or by stimulation of trigeminal receptors on the skin of the face (see Daly & Angell-James, 1975). It has also been reported that cardiovascular responses during carotid chemoreceptor stimulation can be modified by concomitant changes in baroreceptor afferent activity, so that hypotension potentiates these responses (Heistad *et al.* 1975). Finally, hypoxic hypoxaemia by exerting influences on the autonomic reflex pathways and/or on the heart and blood vessels can attenuate cardiovascular adjustments mediated by peripheral chemoreceptors (see Heistad & Abboud, 1980).

CENTRAL CHEMOSENSITIVITY

The possibility of the existence of central chemosensitivity has attracted the interest of physiologists for some considerable time. Indeed, administration of various substances to the IV ventricle of the brain has been known for more than 50 years to affect ventilation (Clementi, 1929; Nicholson & Sobin, 1938) and numerous sites of action by these substances have been postulated (see Leusen, 1972).

Location of central chemosensitivity

As already pointed out, the findings of Leusen (1954*a*, *b*), that hyperventilation occurred in response to elevations in the P_{CO_2} or the H^+ concentration of the artificial cerebrospinal fluid perfusing the cerebral ventricles, focused attention on the role of cerebrospinal fluid in the regulation of respiration. Prompted by these findings, several investigators attempted to locate the site of central chemosensitivity using a variety of experimental approaches including perfusion of the IV ventricle (Loeschcke, Koepchen & Gertz, 1958), local application of pledgets soaked in buffers to the surface of the brain stem (Mitchell *et al.* 1963), direct application of solutions to the surface of the brain stem (Hori, Roth & Yamamoto, 1970), local superfusion of the ventral surface of the medulla (Schlaefke, See & Loeschcke, 1970), local electrical stimulation (Loeschcke *et al.* 1970; Trouth, Loeschcke & Berndt, 1973) and local cold block (Schlaefke & Loeschcke, 1967; Schlaefke *et al.* 1969). The results of these investigations indicated that central chemosensitive structures are located in two areas on the ventrolateral surfaces of the medulla (see Mitchell *et al.* 1973; Schlaefke, 1981). Stimulation of these areas (see Fig. 2), initially designated as areas M and L but now referred to as the rostral and caudal chemosensitive zones, were shown to induce ventilatory and circulatory changes (Loeschcke *et al.* 1970). Another area, located between these two chemosensitive zones is also considered to have a role in central chemosensitivity (Schlaefke *et al.* 1970). This intermediate zone (area S) is supposed to represent the location where afferent fibres from the two chemosensitive zones join and project further to the neurones of the respiratory and cardiovascular controllers within the medulla (see Schlaefke, 1981).
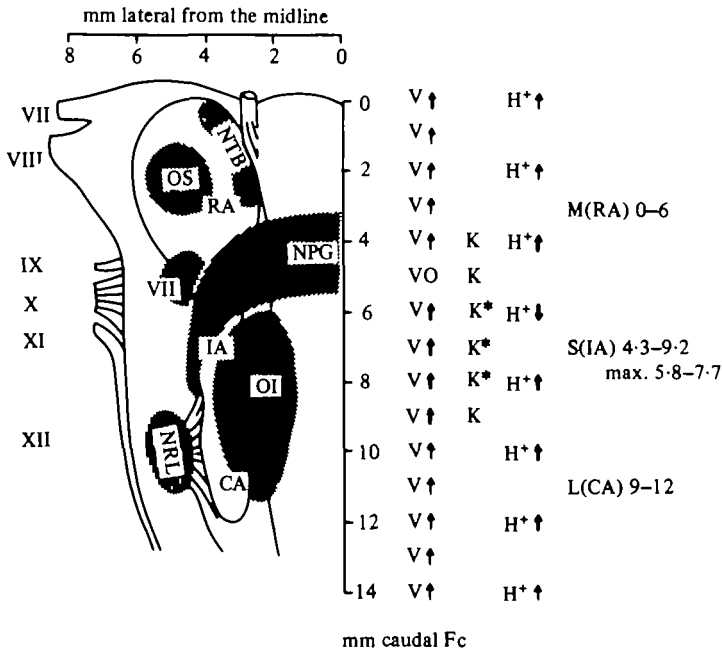
Fig. 2. Left side: Scheme of ventral surface of the medulla oblongata of the cat. VII-XII cranial nerve roots. O, Foramen caecum (Fc). Projected on the surface: NTB, nucleus trapezoid body; OS, superior olive; NPG, paragigantocellular nucleus; OI, inferior olive; NRL, lateral reticular nucleus; VII, VIIth nerve nucleus. Right side: Strongest respiratory responses were elicited from 3 mm lateral of the midline and at points in different caudal distances from the foramen caecum. V for electrical stimulation; K for cold block; H^+ for local superfusion with artificial cerebrospinal fluid of varied pH. Arrows upward, increase; arrows downward, decrease of tidal volume. O, almost no change. Maximal responses to electrical stimulation: o and 11 mm caudal of Fc. K*: largest effect of cold block. The rostrocaudal extension from M, S, and L areas is given. (From Schlaefke, 1981. By permission.)

Morphological and electrophysiological studies

The demonstration by physiological studies of the possible location of central chemosensitive areas on the ventral medullary surfaces was followed by histological investigations of these areas for the purpose of identifying the elements responsible for chemoreception (see Schlaefke, 1981). A number of neurones were shown to be located within the ventral medullary surface layers in the three areas considered to be involved in chemoreception and efforts were made to link the histological findings with physiological results. Of particular interest in this context are the microelectrode recordings of activity from neurones located in the superficial layers of the ventrolateral medulla. In all three relevant areas, activity was recorded from superficially located neurones and a relationship between variations in the pH of the cerebrospinal fluid and the frequency of firing of these neurones was demonstrated in a number of studies (Shimada, Trough & Loeschcke, 1969; Schlaefke *et al.* 1975; Pokorski, Schlaefke & See, 1975; Prill *et al.* 1975). It is of some relevance to point out at this stage that experiments, in which H^+ were iontophoretically applied to the interstitial fluid in the vicinity of the respiratory neurones in the medulla while recording their

.activity, failed to show any increase in the discharge rates of these neurones during this procedure (Marino & Lamb, 1975), and these findings add further support to the hypothesis that central chemosensitivity does not reside in the medullary respiratory neurones but rather in separate chemoreceptive structures.

Results at variance with those described above were obtained by other investigators who failed to observe changes in the activity recorded from neurones within the ventral medullary surfaces in response to variations in pH, and even found considerable difficulty in locating any active neurones in this area (Lipscomb & Boyarski, 1972). These workers and others (Cragg, Patterson & Purves, 1977) have expressed doubt about the superficial location of central chemosensitivity.

Blood supply to the brain stem and central chemosensitivity: Studies of the blood supply to the ventral medullary surfaces have produced an alternative hypothesis concerning the source of central chemosensitivity. Cragg *et al.* (1977) found a close relationship between the density of blood vessels and the location of the putative chemosensitive areas located rostrally and caudally (areas M and L). This finding was taken to indicate that the respiratory responses to chemical stimuli applied to these areas are not due to activation of any specific chemosensitive structures in the ventro-lateral medullary surfaces, but are rather the consequence of the direct action of blood-borne chemical stimuli on deeper medullary elements.

Central chemosensitivity: effects on ventilation

Studies on the ventilatory changes associated with changes in the chemical composition of the cerebrospinal fluid perfusing the cerebral ventricles (see Leusen, 1972) have been extended by investigations in which end-tidal CO_2 was maintained constant. Pappenheimer *et al.* (1965) perfused the cerebrospinal fluid spaces in unanaesthetized goats with solutions of varying bicarbonate concentrations ($[HCO_3^-]$) and calculated that, at a given point on the HCO_3^- gradient from cerebrospinal fluid to the blood, ventilation followed a single function of pH whatever the $[HCO_3^-]$ in the perfusate or the content of CO_2 inhaled. The conclusion reached from these studies is that ventilation is a unique function of H^+ concentration in the vicinity of the central chemosensitive elements. As previously discussed, this conclusion, indicating a lack of contribution by peripheral chemoreceptors to the ventilatory responses during hypercapnia and acidosis, is not universally accepted.

The importance of timing of chemical stimuli arriving at the carotid chemoreceptors in relation to the current phase of respiration has been previously referred to. Recent investigations indicate the possibility of a similar behaviour (phase-coupling) occurring centrally. Thus, Marek *et al.* (1978) reported that electrical stimuli delivered to the ventrolateral medulla during inspiration markedly potentiated that inspiration, a finding that has been confirmed by Mikulski & Trebski (1982) using direct dynamic application of chemical stimuli to the same areas. However, administration via a vertebral artery of chemical stimuli during inspiration has been shown to lessen inspiratory effort and may even promote expiration (Hanson, Nye & Torrance, 1978). Nonetheless, if we assume that changes in P_{a, CO_2} and pHa can rapidly affect cerebro-spinal and cerebral interstitial fluid compositions, then the participation of central

chemosensitive elements in eliciting ventilatory responses to dynamic stimuli could be of considerable importance.

To summarize the current knowledge on central chemosensitivity it can be stated that, although it is widely accepted that alterations in the chemical composition of the cerebrospinal fluid can profoundly affect ventilation, there is still doubts concerning the location of central chemosensitive elements as well as the mechanisms by which these elements excite ventilation.

INTERACTION BETWEEN PERIPHERAL CHEMORECEPTORS AND CENTRAL CHEMOSENSITIVITY

Interactions between peripheral and central chemosensitive mechanisms in the regulation of respiration during hypoxia, hypercapnia or a combination of both has been an area of research for a number of years (see Torrance, 1968; Cunningham, 1974). Despite extensive investigations some problems still remain unresolved. In this article we will briefly deal with two of these unresolved problems.

Ventilatory responses during hypoxic hypoxaemia: The demonstration by Haldane and his colleagues (Haldane & Smith, 1893; Haldane & Priestley, 1905) that hypoxic hyperventilation in human subjects did not occur until the oxygen content of the inspired air was reduced below 14% or so (P_{a, O_2}, 50–60 torr.) has been fully confirmed in subsequent studies (see Torrance, 1968). On the other hand, it has previously been pointed out in this article that carotid chemosensory activity in anaesthetized cats undergoes a steep increase as P_{a, O_2} is reduced below normoxic levels (P_{a, O_2}, 90–100 torr.). While care needs to be exercised in extrapolating results from one species of animal to another and from anaesthetized to unanaesthetized situations, there is evidence that during mild hypoxia (P_{a, O_2}, 60–90 torr.) peripheral chemoreceptor activity does increase in human subjects as it does in the cat. This evidence was provided by the use of the single breath oxygen test as an evaluation of the ventilatory drive mediated by peripheral chemoreceptors (Dejours *et al.* 1958). Use of this test, either as a single breath of oxygen or in other modified forms, demonstrated that peripheral chemoreceptors provide a drive to ventilation that is small in eupnoea but becomes substantially greater in mild hypoxia (Dejours *et al.* 1958; Downes & Lambertsen, 1966; Honda *et al.* 1979). These evaluations of peripheral chemoreceptor drive assume that the bolus of hyperoxic blood following the short-duration administration of oxygen acts only on these receptors so as to suppress ventilation, and evidence has been presented that this is so (see Dejours, 1963).

Changes associated with hypoxia such as central depression, increase in brain stem blood flow, desaturation alkalosis and hypocapnia, have been proposed as explanations for the lack of or diminution of ventilatory responsiveness in the face of enhanced peripheral chemoreceptor reflex drive (see Heymans & Neil, 1958; Cherniack, Edelman & Lahiri, 1971, Lee & Milhorn, 1975). In mild hypoxia, such changes could produce a reduction in central drive to respiration sufficient to balance the increased peripheral chemoreceptor drive. However, in the range of P_{a, O_2} levels associated with ventilatory unresponsiveness during mild hypoxia, these changes would seem to be too small, at least individually, to significantly affect central drive.

Inhibition of chemoreceptor activity mediated by efferent nerves supplying the carotid bodies could also be a factor influencing ventilatory responsiveness in mild hypoxia. It has been shown that increased activity of sinus nerve efferent fibres occurs during hypoxia, due in part to elevated chemosensory discharges originating from the ipsilateral carotid body (Neil & O'Regan, 1971 *b*), and in part to central excitation (Biscoe & Sampson, 1968). Moreover, hypocapnia, increased alkalinity of cerebro-spinal fluid, and possibly increased cerebral blood flow, conditions associated with hypoxia, also enhance sinus nerve efferent discharges (see Majcherczyk *et al.* 1980). There is evidence that an increased sinus nerve efferent activity during hypoxia does, indeed, inhibit carotid chemoreceptor activity (Sampson & Biscoe, 1970; Neil & O'Regan, 1971 *b*) and, furthermore, it has also been shown that this inhibitory effect can be present even in mild hypoxia. As shown in Fig. 3, taken from Neil & O'Regan (1971 *b*), the removal of centrifugal influences mediated by the sinus nerve was followed by an elevation of ipsilateral chemosensory discharges in an anaesthetized cat artificially ventilated with 15% O_2. From a recent report it appears that carotid chemoreceptors are also inhibited by an increased sinus nerve efferent activity in chronic hypoxia (Smatresk *et al.* 1981).

While these studies do point to a role for sinus nerve efferent fibres in modifying carotid chemoreceptor responses to hypoxia, single breath oxygen tests in human subjects argue against this role being of crucial importance in the determination of ventilatory unresponsiveness in mild hypoxia. It might also be added that sympathetic fibres supplying the carotid body can also mediate chemoreceptor inhibition (O'Regan, 1981) but the importance of this inhibitory effect, and the circumstances in which it is invoked have yet to be elucidated.

Ventilatory responses during hypoxia and hypercapnia: Several workers have at-tempted to assess the role of peripheral and central chemosensitive mechanisms in the overall response of ventilation to various combinations of hypoxia and hypercapnia, but the results obtained in different investigations do not agree (see Cunningham, 1974). The problem is difficult to solve and several factors need to be considered.

Various techniques have been employed to study this problem starting from investigations of the effects of denervation of the peripheral chemoreceptors on ventila-tory responses to combined hypoxic and hypercapnic stimulation. This method, how-ever, is not selective enough since section of the nerves supplying the peripheral chemoreceptors, not only deprives the animal of the chemoreceptor input to the brain, but also interrupts baroreceptor afferents and vagal afferents from the lung (if the vagi are sectioned). It also excludes the negative feedback mediated by efferent fibres coursing in the sinus and aortic nerves (see O'Regan, 1977).

The influence of central chemosensitivity on peripheral chemoreceptor drive was investigated by Loeschcke *et al.* (1963) who found that the ventilatory response to electrical stimulation of the sinus nerve was enhanced by central hypercapnia. Other studies, however, indicate that the interaction between central and peripheral drives is less than additive (Gesell, Lapides & Levin, 1940; Wiemer *et al.* 1965). Results obtained in experiments in which the sinus nerve was electrically stimulated during hypoxia and hypercapnia could be misleading since baroreceptor as well as chemo-receptor afferent fibres may have been activated. It is known that increased baro-
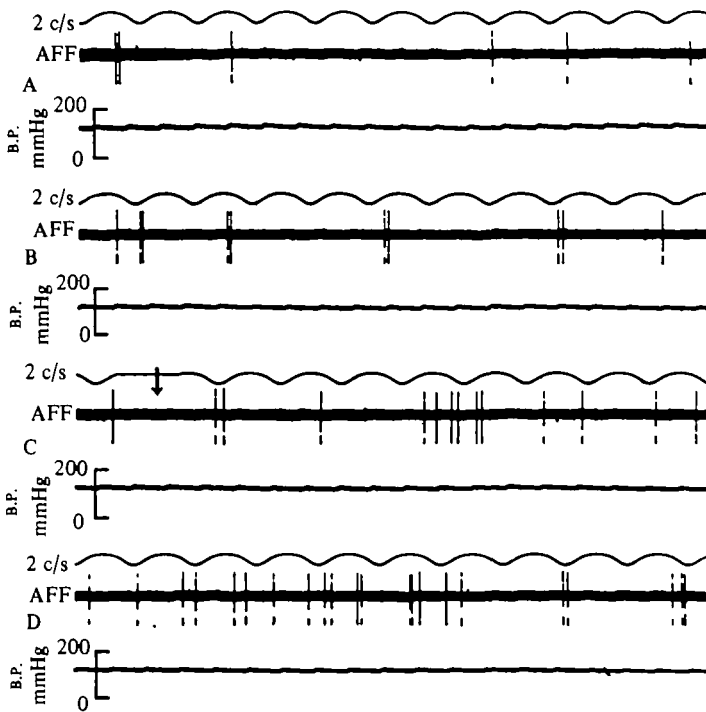
Fig. 3. The effects of section of the left sinus nerve (central to the afferent slip) on the chemore-
ceptor afferent activity (AFF) recorded from a filament of the same nerve. A, recording taken
during artificial ventilation with air; B, recording taken 75 s after the onset of artificial ventila-
tion with 15 % O₂; C, continuous with B (nerve cut at the arrow); D, recording taken 20 s
after nerve section; cat still artificially ventilated with 15 % O. 2 c/s, time marker; B.P.,
systemic arterial blood pressure. (From Neil & O'Regan, 1971 b. By permission.)

sensory activity can inhibit respiration (see Heymans & Neil, 1954) so interpretation
of the influences exerted during sinus nerve stimulation could be difficult to interpret.

Introduction of the isolated carotid sinus preparation permitting the carotid chemo-
receptors to be perfused with solutions having controlled values of P_{O_2}, P_{CO_2} and pH
overcame some of these problems. Using this technique, Lee & Milhorn (1975) con-
cluded that hypoxia depresses ventilation centrally when carotid chemoreceptor drive
is maintained constant at normal and elevated levels of discharge. They also found
that the central ventilatory response to CO_2 was depressed by centrally acting hypoxia,
and that this depression could be reduced by an increase in carotid chemoreceptor
drive. On the other hand, Adams, Attinger & Attinger (1978), using mild stimuli and
the same technique, found that centrally acting hypercapnia and peripherally acting
mild hypoxia combined synergistically on ventilation. Although these investigators
isolated both carotid sinuses they did not denervate the aortic chemoreceptors which
could have affected some of the responses they obtained.

As previously discussed hypoxia and hypercapnia interact in a multiplicative
manner within the carotid chemoreceptors and the question arises whether this
peripheral interaction can fully account for ventilatory responses during asphyxia or

do central chemosensitive mechanisms also contribute? Lahiri & DeLaney (1975b) concluded from their investigations that stimulus interaction between hypoxia and hypercapnia taking place at the peripheral chemoreceptors could not wholly account for stimulus interactions of ventilation. Some central interaction was implied but it depended on the central levels of P_{O_2} and P_{CO_2}.

In CBR subjects, hypoxia does not affect the slopes of the steady-state ventilatory responses to hypercapnia indicating that this organ, when present, contributes the total hypoxic-hypercapnic interaction on ventilation (see Whipp & Wasserman, 1980). Further investigation is needed to settle the disagreements which exist in relation to interactions between peripheral and central chemosensitive elements.

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