REFLEXES ARISING FROM THE ARTERIAL CHEMORECEPTORS

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This short review gives a general survey of the reflex effects of the excitation of the arterial chemoreceptors. It focuses on responses that increase minute ventilation and those that determine the distribution of blood flow within the cardiovascular system, but also touches on influences that occur alongside these. Particular emphasis is given to discussion of the role of the carotid bodies in the generation of exercise hyperpnoea. More comprehensive coverage of this material may be found in reviews by O'Regan and Majcherczyk (1982), Eyzaguirre et al. (1983), Daly (1984), Fitzgerald & Lahiri (1986), and Cunningham (1987). The role of the carotid body in acclimatization to high altitude is covered by Bisgard's chapter in this book.

THE DRIVE TO BREATHE FROM ARTERIAL CHEMORECEPTORS

It is easy to arrange for the arterial chemoreceptors to be the sole source of the drive to breathe. This can be done by allowing an anaesthetized, hypoxic animal to hyperventilate so that its arterial PCO_2 is lowered to a value below the threshold for the reflex ventilatory effects of the central chemoreceptors. The results of such an experiment are shown in Fig 1 where the discharge of a single chemoreceptor fibre in a hypoxic, hypocapnic cat is displayed above the pneumotachogram before and after a breath of 100% oxygen. After a 4s lung-to-carotid body circulation delay the chemoreceptor is silenced, the ongoing inspiration is terminated, and apnoea continues until the combined drive from central and peripheral chemoreceptors has risen sufficiently for breathing to return. This demonstration that the arterial chemoreceptors can assume complete responsibility for the drive to breathe requires that conditions be rigged in their favour i.e. that the animal is hypocapnic and that its 'wakefulness' drive is abolished by anaesthesia, but such conditions are not beyond the bounds met in clinical situations. Furthermore they emphasize that the primary reflex role of the carotid body is to sustain ventilation in hypoxia. They also emphasize the value of the Dejours test, the abrupt surreptitious silencing of arterial chemoreceptor discharge by one or two breaths of 100% oxygen This is the most satisfactory way of assessing the reflex power of the arterial chemoreceptors at any given moment because it pre-empts the excitatory input from the central chemoreceptors that intervenes to replace it (Perret, 1960)

Such pre-emption is important because a rise of only 1 or 2 Torr in medullary PCO_2 can excite the more slowly responding central chemoreceptors to contribute an extra drive equal

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to the entire resting ventilation It is hard to measure a rise in PCO_2 as small as this from the end-tidal or even from arterial blood gases, so longer term experiments, in which central PCO_2 has been given time to rise, often do not satisfactorily assess arterial chemoreceptor drive Experiments in which the carotid bodies are removed surgically, or silenced by the *continuous* breathing of a hyperoxic gas mixture fall into this category Another, more complicated technique for estimating the contribution that the arterial chemoreceptors make to the resting drive to breathe involves vascular isolation of the central and peripheral chemoreceptors so that the gas tensions of the blood perfusing them can be controlled independently (Berkenbosch et al , 1979a) These elegant and technically demanding experiments suggest that in the anaesthetized cat about 40% of the euoxic drive to breathe comes from the carotid bodies The rat may rely on its peripheral chemoreceptors for as much as 50% of its resting drive (Cardenas & Zapata, 1983), and this includes a small contribution from aortic and abdominal chemoreceptors (Martin-Body et al , 1985, Marshall, 1987)

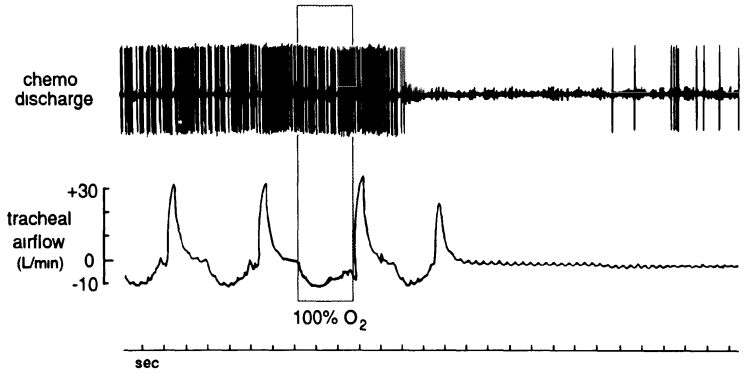

Figure 1. Chemoreceptor discharge and tracheal airflow responses to inspiration of 100% oxygen in an anaesthetized hypoxic, hypocapnic cat Traces from top down chemoreceptor discharge, tracheal airflow and time scale The shaded box marks a single breath of 100% oxygen Four to five seconds later arterial chemoreceptor discharge is silenced and apnoea starts

The arterial chemoreceptors are the only source of the extra ventilatory drive in hypoxia In man the carotid body alone contributes essentially all the hypoxic ventilatory drive, and this is shown in Fig 2 where intact subjects double their isocapnic ventilation in response to a reduction of alveolar PO_2 to 50 Torr, while subjects whose carotid bodies have been removed, but whose aortic bodies are intact, do not respond to the same challenge The dog receives a small ventilatory drive from its aortic bodies (Daly & Ungar, 1966, Hopp et al , 1991) but this amounts only to about one seventh of the combined drive from both sets of arterial chemoreceptors

CARDIOVASCULAR ADJUSTMENTS TO HYPOXIA

The aortic bodies are widely thought to be more important than the carotid bodies in the reflex control of the circulation (Comroe & Mortimer, 1965, Daly & Ungar, 1966) They elicit reflex vasoconstriction which redistributes blood flow away from robust tissues such as the kidney, gut and resting muscle, towards the heart and brain, organs which cannot survive without a continuous supply of oxygen A major component of this reflex redistribution of blood flow during stimulation of the arterial chemoreceptors is illustrated in Fig 3 where the injection of sodium cyanide, which powerfully stimulates their discharge, halves femoral blood flow to hind limb skeletal muscle while it transiently stimulates breathing The coincident bradycardia, which spares the oxygen needs of the heart, is

modest in this panel but if breathing is inhibited by stimulation of the superior laryngeal nerve, or by passing water over the nasopharynx (Fig 3B), the bradycardia can become extreme This powerful reflex inhibition of heart rate, which occurs by the excitation of vagal motoneurones innervating the sino-atrial node, is appropriate when chemoreceptor excitation fails to bring more oxygen into the lungs and may be viewed as a last ditch attempt to conserve the tissue P_{O_2} of the heart It is very pronounced during diving in animals such as the seal (e g Elsner et al , 1977, Daly, 1984) where it has been shown to depend upon the excitation of peripheral chemoreceptors by experiments in which normal heart rate is restored during a dive by reoxygenation of the carotid body This 'diving reflex', which is also seen in man and which can be dramatic in some individuals (Fig 4), is facilitated by concurrent stimulation by cold water of facial receptors running with the trigeminal nerve The widespread peripheral vasoconstriction combined with bradycardia epitomise the underlying effects of chemoreceptor stimulation upon the cardiovascular system This combination of responses forces most tissues to resort to anaerobic metabolism while it allows the heart and brain to draw on the substantial oxygen stores of venous blood The overriding of bradycardia (and to some extent vasoconstriction) by breathing efforts demonstrates that gating of the reflex effects of peripheral chemoreceptor stimulation adjusts the vascular response to the immediate conditions So long as breathing movements continue to ventilate the lungs, vagal bradycardia is blocked by synaptic inhibition arising from central respiratory neurones The activity of pulmonary stretch receptors excited by inflation of the lungs also contributes to the gating of vagal activity (James & Daly, 1969, Daly, 1991)

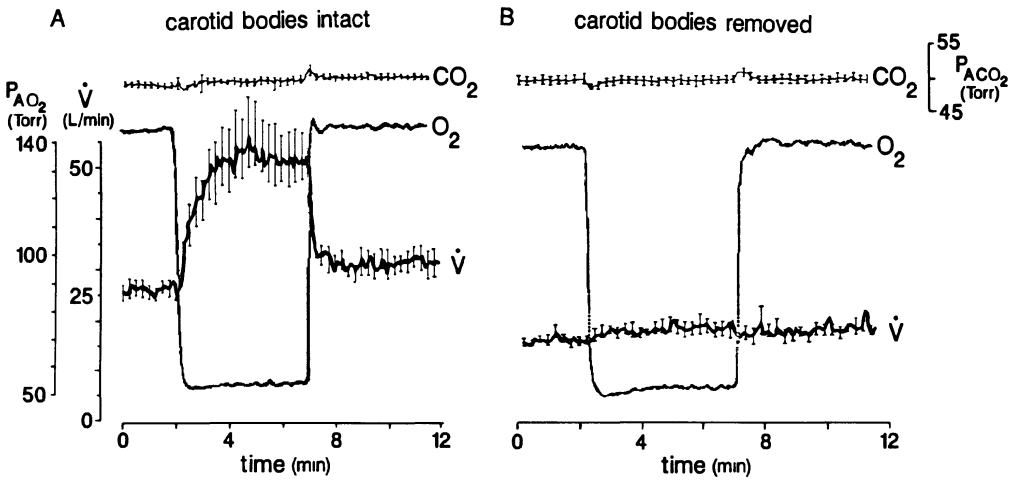

Figure 2. Ventilatory response to hypoxia with CO_2 held constant at 50 Torr in normal subjects and in subjects whose carotid bodies have been surgically removed Both panels show P_ACO_2, P_AO_2 and ventilation (V) Ventilation is doubled by hypoxia in the intact subjects (panel A), but it does not change in subjects lacking carotid bodies (panel B) (Modified with permission from Ward & Robbins, 1987)

The gate that controls the reflex autonomic pathway from arterial chemoreceptors is closed during inspiration, the active part of the respiratory cycle, and this contributes to sinus arrhythmia in which heart rate is slowed only during expiration The abrupt falls in arterial blood pressure in Fig 7 show how opening the gate by the cessation of breathing in response to Dejours tests, can dramatically reduce arterial blood pressure A related gate occludes the reflex slowing of heart rate that results from tonic excitation of baroreceptor

activity but in this case the gate is closed only by central inspiratory activity and not by the discharge of pulmonary stretch receptors (Daly et al , 1986) It too contributes to the generation of sinus arrhythmia The reflex increase in systemic vascular resistance that diverts blood away from robust tissues is attenuated, though not abolished, by inspiratory efforts (James & Daly, 1969) This component is not observable on a breath-by-breath basis because the sympathetic influences responsible for it are mediated by second messenger systems that have slow time constants It is interesting to note that other sensory inputs that elicit bradycardia are not gated out by inspiration For example the reflex inhibition of heart rate which occurs in concert with rapid shallow breathing when pulmonary C-fibres are excited by drugs such as veratridine or phenylbiguanide is unaffected by inspiration (Daly, 1991, Daly & Kirkman, 1989), and similarly the reflex effects of cardiac receptors also bypass the gate (Daly & Kirkman, 1989)

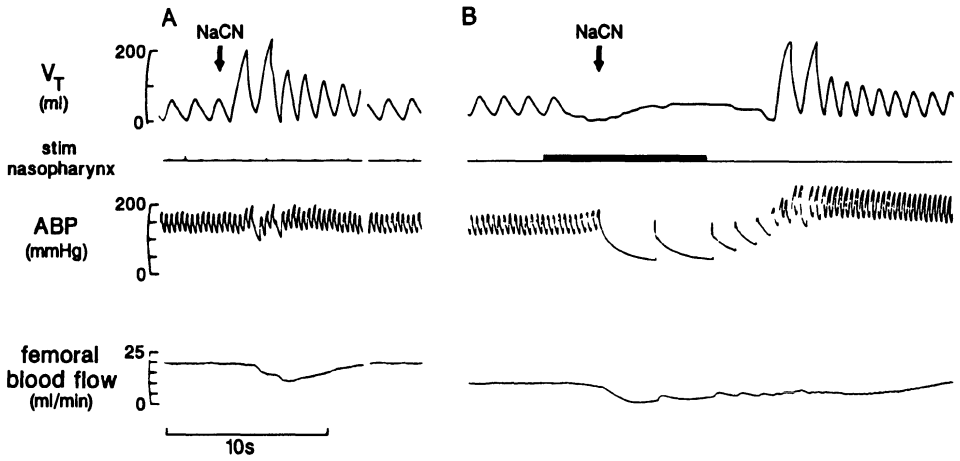

Figure 3. A Intracarotid injection of sodium cyanide (NaCN) in a macaque monkey reflexly increases tidal volume (V_T), reduces femoral blood flow and has little effect on heart rate B When breathing is inhibited by passing water over the nasopharynx (solid marker) the same dose of cyanide causes a marked bradycardia which reduces arterial blood pressure in spite of the raised peripheral resistance that is indicated by the reduction in femoral blood flow (Modified with permission from Daly et al , 1978)

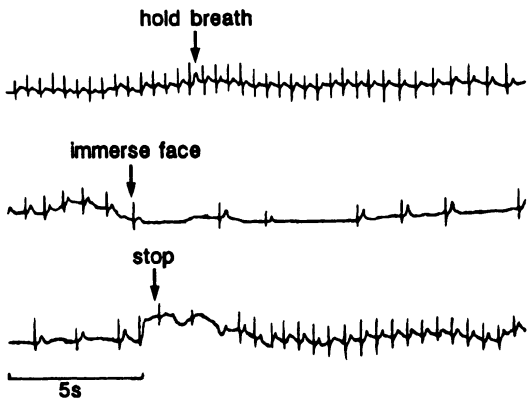

Figure 4. ECG showing the 'diving reflex' in an exercising man Breath hold alone has little effect on heart rate, but immersion of the face in water promptly causes a pronounced bradycardia The traces are continuous (Modified with permission from Stromme & Blix, 1976)

The diversion of blood flow towards the heart and brain does not depend solely on vasoconstriction in robust tissues and the relief of cardiac work by bradycardia The redistribution of flow to the heart and brain is reinforced by reflex vasodilatation of both coronary and cerebral blood vessels and this depends at least in part on the parasympathetic nervous system (Ito & Feigl, 1985, Ponte & Purves, 1974, Hackett et al , 1972) Coronary vasodilatation is complemented by reduced ventricular contractility caused by reduced sympathetic tone, and possibly by increased vagal tone, to the ventricular myocardium (Hainsworth et al , 1979) These responses vividly illustrate that the classical dogma in which the autonomic nervous system seesaws between either parasympathetic or sympathetic activation does not always hold, for parts of both autonomic divisions are activated by chemoreceptor excitation, sympathetic vasoconstriction being combined with vagal bradycardia The simultaneous activation of both autonomic divisions may even be directed at a single target, the sino-atrial node, for O'Donnell and Bower (1992) have shown that when the cat's carotid body is excited by hypoxia, vagal blockade by atropine can turn a parasympathetically mediated 56 beat per minute reduction in heart rate into a sympathetically mediated 28 beat per minute increase Qualitatively similar results have been published by Little and Oberg (1975)

INTERACTION OF CHEMORECEPTOR AND BARORECEPTOR REFLEXES

The cardiovascular components of the arterial chemoreflex can have complex effects on arterial blood pressure This is because the rapidly activated slowing of heart rate tends to reduce blood pressure while the more slowly activated peripheral vasoconstriction raises it It is therefore normal to see a rise in arterial blood pressure when breathing efforts are preferentially gating out the bradycardia, but a fall when the powerful bradycardia of the apnoeic diving reflex is given free rein These changes inevitably elicit substantial changes in the discharge of arterial baroreceptors, so it is not surprising to discover that the reflex effects arising from chemoreceptors are modulated by those from baroreceptors which compete for the same efferent limbs Mancia et al (1976) showed that severely raised baroreceptor discharge can completely override the vascular responses to chemoreceptor stimulation Baroreceptor activation also reduces ventilatory stimulation (Attinger et al , 1976) This effect can be thought of in terms of the matching of overall ventilation and perfusion, for a raised blood pressure can signify an unnecessarily high cardiac output and a reduced need for oxygen transport within both the cardiovascular system and the lungs (e g Wright, 1930, Bishop, 1974, Heistad et al , 1975, Attinger et al , 1976) In man the rise in arterial blood pressure which reflects the increase in total peripheral resistance almost invariably associated with hypoxia appears to be mediated entirely by the carotid body This is shown by the absence of a rise in carotid body resected subjects (Honda, 1992)

OTHER REFLEX EFFECTS FROM ARTERIAL CHEMORECEPTORS

The excitation of arterial chemoreceptors has reflex effects on variables that are often overlooked in discussions of cardiovascular and ventilatory control These include a threefold increase in the rate of tracheal secretion (Davis et al , 1982) which counters the drying influence of increased ventilation, and bronchoconstriction which is normally blocked by reflex bronchial dilatation arising from pulmonary stretch receptors Chemoreflex bronchoconstriction may only be apparent when the airways are sensitized by the inspiration of bronchoconstrictors such as methacholine or by asthma (Denjean et al , 1991) There has also been the suggestion that oxygen's partner in metabolism, glucose, is made more available by release from the liver in response to excitation of the carotid body (Alvarez-Buylla & de Alvarez-Buylla, 1988) This harks back to the now largely forgotten condition of asphyxial hyperglycaemia known to Bernard in the nineteenth century, and studied before the discovery of the arterial chemoreceptors by Macleod (1909) The reflex effects of

arterial chemoreceptor discharge on renal function are complicated by competing reflexes excited by changes in arterial and atrial pressure and by the direct effects of hypoxia on the kidney Further complication is added by the many components of the renal response that are available for alteration These include glomerular filtration rate, filtration fraction, and electrolyte and water reabsorption, each of which may change to give different urine flows and concentrations Complicated influences give complicated responses, reflected by reports that hypoxia may either increase or decrease urine flow and the reabsorption of sodium The results of experiments on anaesthetized animals are matched by those on subjects at altitude, for both diuresis and anuresis are reported (Ward et al , 1989) Honig's group (Honig, 1989) have emphasized the tendency of hypoxia to raise haematocrit rapidly by a natriuretic increase in urine flow, increased reabsorption of plasma in systemic tissues, and reduced thirst The increased excretion of sodium survives denervation of the kidney but not denervation of the carotid body (Karim et al , 1987) so although it originates in the carotid body it has a humoral component and is therefore not strictly a reflex response The purely reflex effects of carotid body stimulation on renal function recorded at constant arterial blood pressure and without systemic hypoxia act by increasing the discharge of the renal sympathetic nerves This preferentially constricts the afferent arterioles, reducing glomerular filtration rate and filtration fraction as well as renal blood flow There is also a concurrent reduction in sodium excretion and urine flow (Karim et al , 1987) It seems therefore that, in the short term, the reflex effects of the carotid body on renal function complement those on the circulations of skeletal muscle, intestine and other splanchnic organs They are primarily concerned with the diversion of blood flow away from the kidney (Al-Obaidi & Karim, 1992), a response that almost inevitably reduces urine flow Humoral influences tending to increase urine flow may become more important when hypoxia is sustained for hours rather than minutes Like their effects on other vascular beds, the arterial baro- and chemoreflexes compete for control of renal function Activation of the former reduces sympathetic tone while activation of the latter increases it If baroreceptor activity is intense it can reveal underlying responses to chemoreceptor activation that are of the opposite sign to those normally expressed, i e excitation of the chemoreceptors now increases urine flow and sodium excretion (Karim & Al-Obaidi, 1993) Raised plasma osmolality has been reported to inhibit the discharge of arterial chemoreceptors in the intact cat (Gallego & Belmonte, 1979) This inhibition contrasts with the excitation reported in isolated carotid bodies (Gallego et al , 1979) and it presumably results from reduction in the resistance of the vessels perfusing the organ The effect requires a physiologically large (5%) change in osmolality before any change in discharge is observed

OSCILLATIONS OF DISCHARGE AND THE DRIVE TO BREATHE

Gating of the reflex effects of chemoreceptor discharge by the respiratory cycle is not confined to cardiovascular responses It can also be seen in the pattern of breathing Here the behaviour of the gate differs from that of its cardiovascular counterpart because instead of closing in inspiration it opens, allowing excitation to have its maximal effect on ventilation during this phase (Black & Torrance, 1971, Eldridge, 1972) Much has been made of the possible significance that this phase-dependent excitation of ventilation by chemoreceptor discharge may have in exercise because it may select parts of the natural oscillation of chemoreceptor discharge that occurs with each breath For example it is possible that, with a four second respiratory cycle and a four or five second lung-to-carotid body circulation delay, the open gate would allow only the troughs of the oscillating chemoreceptor discharge to pass at rest, while the altered respiratory cycle duration and circulation delay of exercise might result in passage of the peaks There is little direct evidence for such an arrangement but if it exists it would enhance the effective mean discharge of chemoreceptors even in the absence of a rise in the true mean level of either discharge or arterial gas tensions (see Cunningham, 1975)

INTERACTION OF VENTILATORY INFLUENCES FROM PERIPHERAL AND CENTRAL CHEMORECEPTORS

The effects of hypoxia and carbon dioxide on chemoreceptor discharge are not simply additive They multiply, giving a fan of response lines, with sensitivity to CO_2 increasing in hypoxia (Fig 5) This fan is similar to that observed when ventilation is plotted against P_ACO_2, and it is reasonable to ask whether the former can account entirely for the latter or whether there is further interaction in the brainstem between peripheral and central chemoreceptor input The supposition that it may take more than just the fan of discharge to give the fan of ventilation is given substance by the observation that the point at which the CO_2-response lines converge is close to 20 Torr for discharge (in the cat, Fitzgerald & Parks, 1971, Lahiri & Delaney, 1975, Nye & Painter, 1989) and close to 40 Torr for ventilation (in man, Lloyd & Cunningham, 1963) The question is not easily resolved in man because chemoreceptor discharge cannot be recorded, but it appears that in the cat, which has a low resting P_ACO_2, the point of convergence of the ventilatory lines is close to that of discharge (DeGoede et al , 1981) and the fan is generated entirely by the peripheral chemoreceptors (Berkenbosch et al , 1979b) In this species the ventilatory responses to excitation of peripheral and central chemoreceptor inputs are therefore purely additive (Heeringa et al , 1979, Berkenbosch et al , 1984) However, the situation may not be so simple in man because, as pointed out by Robbins (1989), although ventilation is insensitive to CO_2 in hypocapnia, giving the 'dogleg' of Fig 5, it is nevertheless excited by hypoxia in this range This suggests that in man the peripheral chemoreceptors are active in hypocapnia below the point at which the ventilatory lines converge i e below the threshold at which the reflex effects of the central chemoreceptors appear The cat is, appropriately, reported by some (Berkenbosch et al , 1984) to lack a dog-leg, though Grunstein et al (1975) do show one

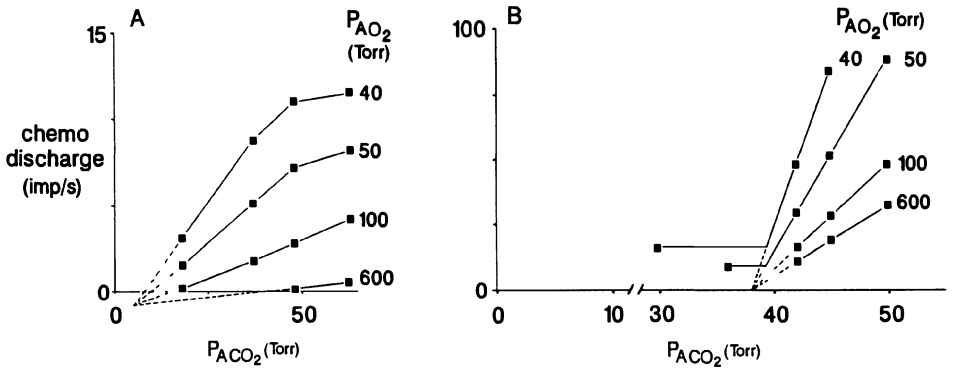

Figure 5. Hypoxic enhancement of CO_2-sensitivity of carotid body discharge (A) and of ventilation (B) giving similar fans Discharge was recorded in the cat (Nye & Painter, 1989) and ventilation was recorded in man (Lloyd & Cunningham, 1963) B shows the 'dog-legs' that occur below ca 40 Torr PCO_2 Here hypoxia has little or no effect on ventilatory sensitivity to CO_2 but it does increase ventilation

THE ARTERIAL CHEMOREFLEX IN EXERCISE

During exercise, ventilation (V_E) increases in direct proportion to CO_2 production (VCO_2) until the intensity of exercise is greater than approximately 60% of maximum achievable work rate At this point V_E increases disproportionately to increases in VCO_2 This point is known as the 'ventilatory threshold' or 'anaerobic threshold' because it coincides with the reduction in arterial pH caused by the release of lactic acid from anaerobic metabolism The arterial chemoreceptors are shown to be responsible for this threshold as subjects without carotid bodies (Wasserman et al , 1975) and subjects lacking respiratory

chemoreception (Shea et al , 1993) fail to compensate for the build-up of metabolites by hyperventilating - they lack an anaerobic threshold It is now well established that exercise increases the 'hypoxic sensitivity' of the arterial chemoreflex in direct proportion to the rise in VCO_2 (Douglas et al , 1913, Cunningham et al , 1966, Weil et al , 1972) and that this increased sensitivity determines the position of the anaerobic threshold This concept is illustrated in Fig 6 which shows observations made by Douglas at the turn of the century In these the slope of the V_E/VCO_2 relationship in exercise was steeper at altitude (P_AO_2 ca 60 Torr) than it was at sea level However, the mechanisms that regulate the increased hypoxic gain of the arterial chemoreflex in exercise have not been fully resolved

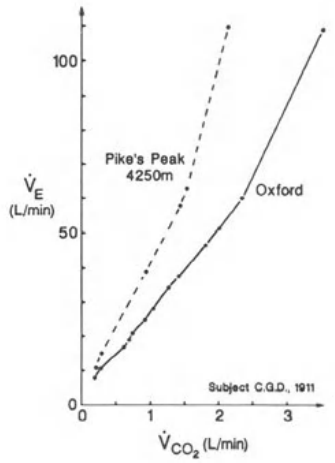

Figure 6. The ventilatory response of C G Douglas to several intensities of exercise near sea level (Oxford, 55 m) and at an altitude of 4250 m (Pike's Peak, Colorado, ca 60 Torr P_AO_2) Note that the ventilatory response to exercise is markedly increased by hypoxia

EXERCISE BELOW THE ANAEROBIC THRESHOLD

It is still widely believed that light exercise causes little change in the sensitivity of the arterial chemoreflex, however Cunningham et al (1966) observed that light exercise can potentiate the sensitivity of the carotid bodies, noting that the ventilatory response to two breaths of hypoxia was greater in exercise than at rest This idea was further developed and quantified by Weil et al (1972) who showed that very mild exercise enhances the hypoxic ventilatory drive, an effect that increases in proportion to the intensity of exercise (Fig 7) If a two or three breaths of 100% oxygen (the Dejours test) are given during light steady-state exercise, below the anaerobic threshold so there is no lactic acid to excite the arterial chemoreceptors, ventilation is reduced within a few seconds (Perret, 1960, Dejours, 1962) This shows that the absolute contribution that the arterial chemoreceptors make to ventilatory drive increases progressively as ventilation rises towards its new steady state (Cunningham et al , 1968) The progressively increasing role of the carotid bodies during this rise is underlined by the observation that the rate of rise is slower in hyperoxia (Griffiths et al , 1986) and after surgical removal of the carotid bodies (Wasserman et al , 1975) Furthermore hypoxia increases the time constant of the transient The transient is also slowed by beta adrenergic blockade and this has led some workers to propose that the slowed ventilatory response is caused by a reduced cardiac output - cardiodynamic hyperpnoea (Petersen et al , 1983) However, beta blockade markedly reduces carotid body discharge and its sensitivity to both hypoxia (Folgering et al , 1982) and potassium (Paterson & Nye, 1988), so it is likely that the slower rise in ventilation results from direct inhibition of the carotid body rather than from a lack of excitation acting indirectly via the heart

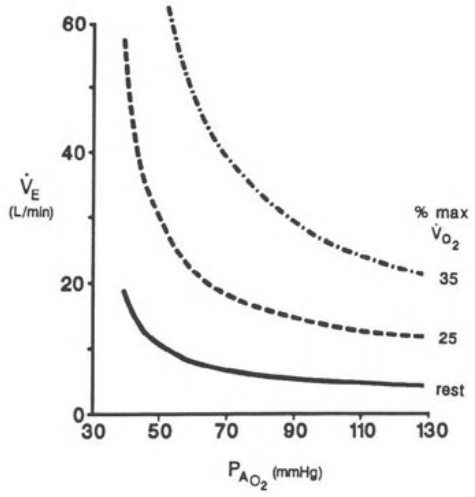

Figure 7. Ventilatory response to hypoxia during mild to moderate levels of exercise in man. Sensitivity to hypoxia is increased markedly at levels of oxygen consumption that are not associated with excitatory changes in the pH, PCO_2 or PO_2 of arterial blood (Reproduced with permission from Weil et al. 1972)

Interestingly, subjects with congenital central hypoventilation syndrome who have no functional peripheral or central chemosensitivity have a normal ventilatory response in aerobic exercise (Shea et al., 1993): they maintain isocapnic buffering without chemical feedback. This shows that respiratory chemoreception is not essential for the control of ventilation during aerobic exercise, an observation which highlights the redundancy that nature has built into the respiratory control system.

EXERCISE ABOVE THE ANAEROBIC THRESHOLD

It is generally accepted that the increase in ventilatory sensitivity to VCO_2 above the anaerobic threshold is mediated by the carotid bodies (Wasserman et al., 1975), an idea supported by the observation that subjects whose carotid bodies have been removed, and subjects born insensitive to changes in arterial blood gas tensions (Shea et al., 1993), do not have an anaerobic threshold. Acidosis is traditionally regarded as the prime signal that stimulates the carotid bodies to cause this extra increase in ventilation. However, many studies now cast doubt on whether acid is the only, or indeed the mandatory stimulus for this response. For example, patients with McArdle's syndrome cannot produce acid during exercise yet they still have the well established threshold (Hagberg et al., 1982) and subjects who have undergone glycogen depletion to reduce the amount of substrate available for lactic acid production also have an anaerobic threshold that is independent of changes in arterial pH (Heigenhauser et al., 1983; Busse et al., 1991). Using the Dejours test to assess ventilatory drive from the arterial chemoreflex during air-breathing ramp increases in work rate presents a paradox, because it results in very little reduction in ventilation even at exercise intensities that result in substantial increases in lactic acid concentration (unpublished observations by Burleigh and Robbins from our Laboratory). This suggests that either the carotid bodies are not involved in the unsteady-state ventilatory response to exercise, that hyperoxia does not silence their activity during incremental exercise, or that other inputs can very quickly assume the role of the carotid body. However, when the Dejours test is given in heavy steady-state, air-breathing exercise there is an abrupt and large reduction in ventilation before there are any significant changes in the concentration of lactic acid (Asmussen & Nielsen, 1946).

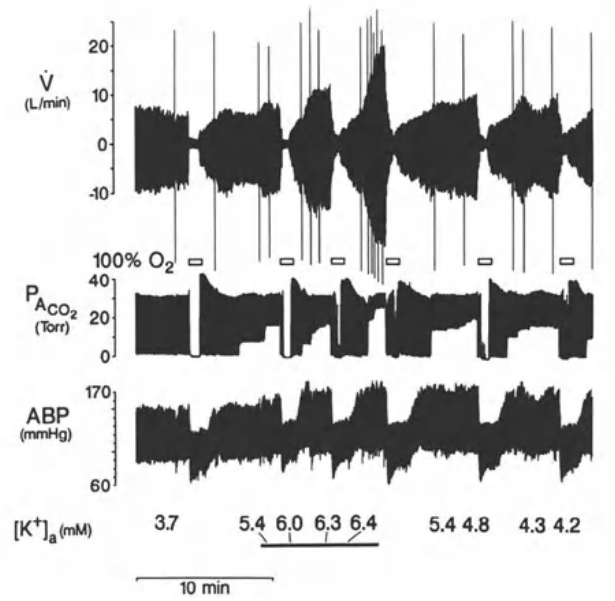

Figure 8. Ventilatory response of a hypoxic (P_aO_2 39 Torr) rhesus monkey to abrupt switches of 100% oxygen (hollow boxes) before, during and after a KCl infusion (horizontal bar) Traces from the top down tracheal airflow, alveolar PCO_2 and arterial blood pressure (ABP) CO_2 was added to the inspirate to keep P_ACO_2 constant when ventilation rose A switch to 100% O2 virtually abolished the excitation of ventilation by hyperkalaemia When the KCl was stopped, ventilation decreased with the fall in $[K^+]_a$ (Reproduced with permission from Paterson et al , 1992)

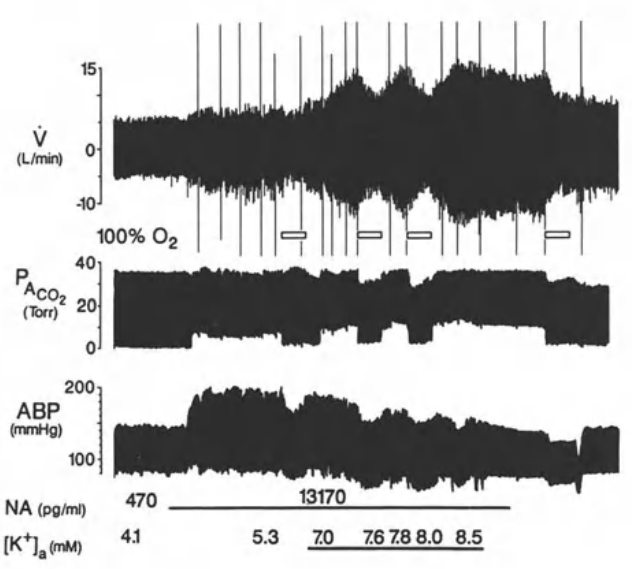

Figure 9. Ventilatory response of a euoxic (P_aO_2 100 Torr) monkey to abrupt switches of 100% oxygen (hollow boxes) during concurrent infusions of noradrenaline (NA) and KCl (horizontal bars) Traces from the top down tracheal airflow, alveolar PCO_2, arterial blood pressure (ABP) Note that NA caused a small increase in ventilation and that hyperoxia had little effect on ventilation during the NA infusion When KCl was added in the presence of the NA infusion, there was a marked increase in ventilation which was reduced by hyperoxia (Reproduced with permission from Paterson et al , 1992)

This led to the idea that a chemical released from working muscle, an 'anaerobic work substance', excites the carotid bodies The short latency of the ventilatory response to the Dejours test was accounted for by assuming that the substance was rapidly inactivated by high oxygen

Recent work has suggested that exercise-induced hyperkalaemia fulfils many of the criteria of the anaerobic work substance Potassium is released from contracting muscle in direct proportion to V_{CO_2} It is well correlated with V_E in normal subjects (Paterson et al , 1989, Busse et al , 1991), in patients with McArdle's syndrome (Paterson et al , 1990) and in glycogen-depleted subjects (Busse et al , 1991) Band et al (1985) first showed that physiological levels of hyperkalaemia excite ventilation by direct excitation of the arterial chemoreceptors in the anaesthetized cat The effect of potassium on chemoreceptor discharge is markedly sensitive to oxygen, being much greater in hypoxia and almost absent in high oxygen (Burger et al , 1988) This makes it behave as if, like the hypothetical anaerobic work substance, it is rapidly inactivated by a rise in arterial oxygen In the decerebrate cat (Paterson & Nye, 1991) and sedated rhesus monkey (Paterson et al , 1992) hyperkalaemia markedly increases ventilation during hypoxia and the Dejours test essentially abolishes its stimulatory effect (Fig 8) Raised plasma noradrenaline also increases ventilation in euoxia, an effect enhanced in the monkey by hyperkalaemia (Fig 9) We have recently observed that the excitation of the cat's carotid body discharge by noradrenaline and hyperkalaemia interact additively (unpublished observation from this laboratory) McLoughlin et al (1992) also report that lactic acid potentiates the discharge of the arterial chemoreflex in hyperkalaemia

THE MECHANISM RESPONSIBLE FOR ENHANCEMENT OF THE ARTERIAL CHEMOREFLEX IN EXERCISE

Several candidates have been considered to be possible contributors to the enhanced role of the carotid body in exercise For example potassium increases the sensitivity of the arterial chemoreflex and interacts multiplicatively with hypoxia to provide a powerful drive to breathe Qayyum et al (1994) observed that modestly raising the concentration of arterial plasma potassium (by ca 1mM), by drinking 64 mmoles of KCl, significantly increases hypoxic ventilation both at rest and in light exercise This provided the first direct evidence that modest rises in plasma potassium can modulate the sensitivity of the arterial chemoreceptor reflex in conscious man

Potassium is not the only chemical factor that can enhance the sensitivity of the ventilatory reflex Both acidosis and raised catecholamines increase chemoreceptor discharge and ventilation (McLoughlin et al , 1992, Cunningham et al , 1963, O'Regan & Majcherczyk, 1982) and the effects of these stimuli are also increased in hypoxia and markedly reduced in high oxygen Thus it would not be surprising to find a three-way interaction among exercise-induced changes in potassium, acid and catecholamines that enhances the sensitivity of the peripheral chemoreflex, the efficacy of this response being modulated by oxygen In addition the peripheral chemoreceptor reflex loop may be enhanced by descending pathways from hypothalamic and cortical projections (Eldridge et al , 1981)

Finally, the contribution that the arterial chemoreflex makes to the control of exercise hyperpnoea is far from settled There are clear species differences that show little role for this reflex in exercise in some animals (e g pony, Forster et al , 1983) However, the Dejours test reveals that, at least in man, the carotid bodies play an important role in the matching of ventilation to metabolic rate in exercise, and that the by-products of heavy exercise modulate the sensitivity of the arterial chemoreflex

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