*Proc. Indian natn Sci Acad.(PINSA)* **B66** Nos 2 & 3 pp 121-130 (2000)

# Arterial Chemoreceptors (Sensing Fall in Oxygen and Role under Physiological Conditions)

ASHIMA ANAND
*Centre for Visceral Mechanisms, Vallabhbhai Patel Chest Institute P.O. Box 2101, Delhi University, Delhi 110007*

(Received on 18 February 2000; Accepted after revision on 23 June 2000)

Arterial chemoreceptors which constitute the body's sensory mechanism for detecting a fall in oxygen in the arterial blood comprise of two kinds of cells and sensory nerve endings present around large blood sinusoids within the organelles referred to as the carotid and aortic bodies. A special feature of these structures is a high blood flow and oxygen consumption rate and which is three times that of the brain tissue. In nature, a fall in arterial oxygen would occur if the partial pressure of the oxygen, in the air being breathed fell below the normal values of 150 mmHg (at altitudes above 3,000 meters) or by a fall in the systemic blood pressure (hypotension) which would reduce blood flow and subsequently, the rate of oxygen flow through these organelles. A third mechanism, would be if the haemoglobin content of the blood fell.

Stimulation of these chemoreceptors reflexly increases respiration and raises systemic arterial blood pressure so as to compensate the fall in available oxygen, to the organism.

There is a disagreement, as to what comprises the stimulus for these receptors in nature and also over the mechanism of transduction of the nerve impulses at the sensory cell site. Since, under physiological circumstances, organisms do not encounter hypoxia naturally at sea-level ( fall in the partial pressure of oxygen in the air breathed), but may experience a fall in blood pressure (postural hypotension) several times during a day's activity it is more likely that hypotension, is the physiological stimulus for the chemoreceptors. One view about the transduction of nerve impulses, in chemoreceptors is, that hypoxia induces secretion of some transmitter substance by the sensory cells which then brings about a depolarization of the nerve endings. The other view, is that the stimulus causes a mechanical deformation of the sensory cell membrane, in much the same way as in most other sensory cells and sets up a nerve impulse. A number of neuroactive substances have been proposed from time to time as transmitter probables. The most pursued are acetylcholine and dopamine. The main shortcoming of this hypothesis is that by using blockers of the proposed transmitter substances or those of the subcellular processes preceding their release, it is not possible to silence the nerve discharge during hypoxia. As the chemoreceptor fibres continue to fire long after the animal is dead, this hypothesis, inadvertently, presumes that the transmitter substances would also continue to be synthesized and secreted to account for this activity. However, the latter contention is untenable given the energy requirements of the cellular events. Thus, there is still no substantiative evidence to support the transmitter-release theory. On the other hand, further work to support the transduction of impulses by mechanical means needs to be undertaken so as to determine the manner in which a fall in arterial oxygen leads to a mechanical deformation of the nerve fibres. In addition, a demonstration of the reversal of effects when the stimulus ceases, would provide further support.

**Key Words : Chemoreceptors, Carotid body, Aortic bodies, Respiration, Blood pressure, Sympathetic outflow, Postural (orthostatic) hypotension, High altitude, Transmitter-release, Mechanosensitive transduction**

## Introduction

In nature, mammals are rarely exposed to life under 'limited-oxygen' conditions after birth. It is only populations living at altitudes above 3,000 meters that are exposed to atmospheric levels of oxygen (80 mmHg) that are below the sea -level values (150 mmHg). Yet, all mammals, from man to mouse, that have been investigated so far (i.e. rat, rabbit, guinea pigs, cats, dogs, goats and humans) possess small structures weighing about a milligram called the carotid and aortic bodies whose sensory nerve endings are exquisitely sensitive to a fall in the available oxygen in the arterial blood perfusing through them. These are the chemoreceptors and were discovered by Heymans & Heymans in 1927 and between the years 1927-31 they, along with their colleagues, described their role in the control of respiration and circulation. Some work has been done to define the role of the arterial chemoreceptors in increasing ventilation in response to hypoxia at altitude (Mathew et al.1983) but the various reports on the mechanisms involved are at variance with each other (Mitchell 1966, Severinghaus 1963, Dempsey et al.1974, Michel & Milledge 1975).

A fall in oxygen, may result from (i) a reduction in the partial pressure of oxygen in the air being breathed (at low barometeric pressure at altitude) leading to a fall in the arterial oxygen tension ($pa_{O_2}$); (ii) a reduction in the rate of oxygen being carried by blood as by a fall in the arterial blood pressure (hypotension) or (iii) by reduction in oxygen content (fall in available haemoglobin e.g. in anemia or as a result of carbon monoxide poisoning). Although in nature, large percentages of carbon dioxide are not encountered normally in the air breathed, Heymans et al. (1930) found at about the same time that the carotid body, also, responded to large increases in the other respiratory gas i.e. carbon dioxide; delivered equilibrated in the arterial blood.

The reflexes that arise as a result of a fall in available oxygen are an increase in respiratory rate and volume, a rise in the systemic blood pressure and cardiac acceleration (Comroe1939, Comroe & Mortimer 1964, Daly &Ungar 1966). Natives of high altitudes are adapted to living in an environment of low ambient oxygen levels and consequently do not breathe at rates higher than normal as unacclimatized individuals do (Severinghaus et al. 1966). In other words, their response to hypoxia is 'blunted' (Chiodi 1957, Milledge & Lahiri 1967). This feature of their physiology has not been incorporated into their genome inspite of living at high altitude for generations - their offsprings born at sea level do not possess this capability. According to Byrne-Quinn et al. 1972, they acquire it only after they have resided continously at high altitude for upto 12 years or so.

## Carotid and Aortic Bodies

The carotid bodies, two in number, are found one each at the bifurcation of the common carotid artery of the left and the right side. The location of the

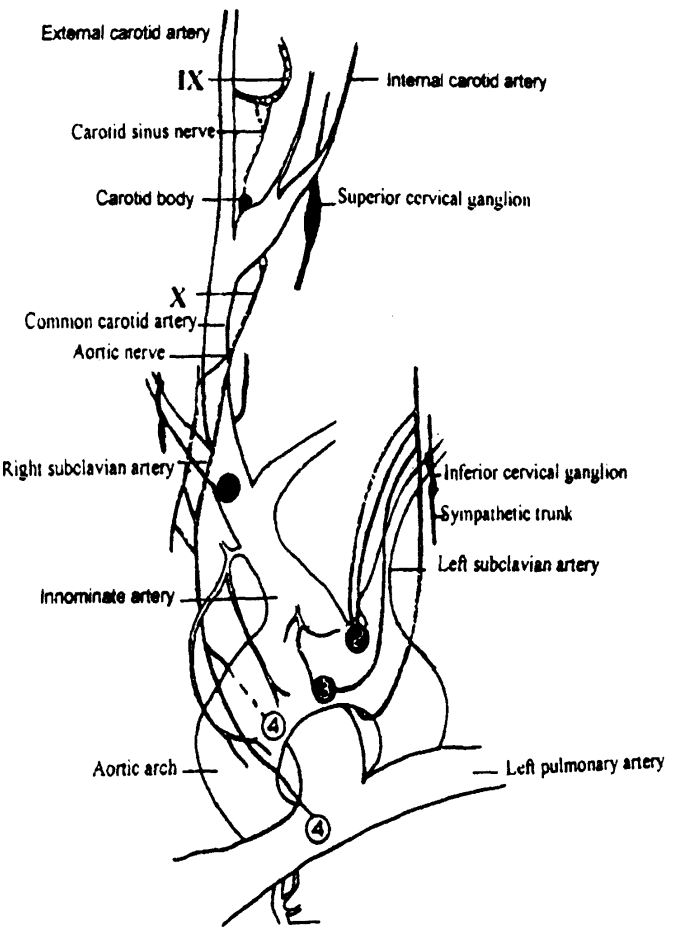


**Figure 1** The location and innervation of the carotid and aortic bodies. The aortic body groups are represented with numerals within circles (1-4); IX- glossopharyngeal nerve; X - vagus nerve.

four aortic bodies, however, is not so specific (figure 1). Of the two connected to the right aortic nerve (a branch of the right vagus or Xth cranial nerve) one is located at the root of the right subclavian artery and the second one is between the aortic arch and the pulmonary trunk .Similarly, of the two connected to the left aortic nerve, one is found at the base of the left subclavian artery and the other one is found on the ventral side of the aortic arch (Coleridge et al. 1967). Structurally the carotid body is a highly vascular organ with two types of cells surrounding fine capillaries or wide sinusoids. Between these cells lie sympathetic fibres and the sensory endings of the carotid sinus nerve which. is a branch of glossopharyngeal or IXth cranial nerve and which supplies both chemoreceptors and baroreceptors.

There are two types of cells present in the carotid and aortic bodies - one has an abundance of mitochondria and is referred to as the type I cell. Evidence from electron microscope studies suggests that this cell, probably, has a high metabolic rate (Ross 1959). The other type of cell has fewer mitochondria and a granular endoplasmic reticulum and characteristic finger-like processes which are folded around type I cells and the nerve fibres. This cell is called the type II or sustentatcular cell. DeCastro observed single nerve fibres branching extensively and ending on several type I cells of different cell clusters and often, single cells receiving more than one nerve fibre (for a description of De Castro's work, *see* Eyzaguirre & Gallego 1975).

## Stimuli

The sensitivity of chemoreceptors to a fall in tissue $p_{O2}(tp_{O2})$ seems to be brought about by a very high oxygen consumption rate of the carotid body (9–45 $\mu l\ gm^{-1}\ min^{-1}$) i.e. three times that of the brain tissue which in turn is maintained by an equally high rate of blood flow through it (0.18 $\mu l\ min^{-1}$) (Daly et al.1954). Though these estimations have been possible only for the carotid body which is more approachable than the four groups of aortic bodies, it is presumed that these values also apply to the latter–mainly, because their responses to arterial hypoxia are identical.

*Carbon dioxide*: Ever since it was suggested about sixty years ago by Heymans et al. (1930), carbon dioxide has been vigorously pursued as a natural stimulus for chemoreceptors (Hornbein et al.1963, Fitzgerald & Parks 1971). Observations on aortic chemoreceptors, however, have failed to demonstrate that within physiological levels of increase, carbon dioxide had any noteworthy excitatory effect on them at all (Paintal & Riley 1966). A recent study on humans (Clements et al.1995) suggested that peripheral chemoreceptors do not contribute to the increase in respiration seen by breathing hypercapnic gas mixtures. Nevertheless, a lot of emphasis has been paid to small increases in chemoreceptor activity within the physiological range of arterial $CO_2$ increase (Lahiri et al.1979, 1980a). Since it had a definite dynamic effect on the carotid chemoreceptors, though not clearly a static one, carbon dioxide came to be regarded as a natural stimulus for both the aortic and carotid chemoreceptors (see Eyzaguirre et al. 1983). Anand and Paintal (1988), attributed the excitation of aortic chemoreceptors, (when seen) by hypercapnia, to a consequence of vasoconstriction in the aortic body brought about by increased sympathetic outflow. They demonstrated this by reducing sympathetic outflow, which resulted in the silencing of the hitherto, active chemoreceptors. However, one wonders how an increase in inspired $CO_2$ / arterial $HCO_3^+$, can be equivalent to any one of the three mechanisms by which available oxygen is reduced in the arterial blood as described in the Introduction. However, the manner whereby the chemoreceptor nerve endings may be stimulated by an increase in $pa_{CO2}$ is described below (see section on 'mechanical-deformation hypothesis').

*The ultimate stimulus:* Anand and Paintal (1990) provided convincing evidence to show that local $pO_2$ and not arterial $pO_2$ is the stimulus for the chemoreceptors. Local $pO_2$ at the receptor site is itself determined by the arterial $pO_2$, the haemoglobin concentration and blood flow rate (which depends on blood pressure). These determine oxygen availability. As has been pointed out in the introduction, the atmospheric oxygen pressure at sea level is adequate for life processes and does not change spontaneously. Thus, the factor that could stimulate chemoreceptors in nature, is a fall in blood flow brought about, physiologically, by a fall in blood pressure.

*Transduction of Nerve Impulses*

Currently pursued, are two views about the mechanism of initiation of nerve impulses at chemoreceptors. The more widely held view is that the stimuli of chemoreceptors cause a release of some transmitter substance from the type I cells of the carotid and aortic bodies that depolarizes the nerve membrane of the sensory nerve fibres leading to a production of the nerve impulse. The other view, is that the stimulus causes a mechanical deformation of the sensory cell which in turn deforms the sensory ending membrane, in much the same way as it occurs in the muscle spindle (Katz 1950), or the Pacinian corpuscle (Lowenstein 1959), and sets up a nerve impulse.

*'Transmitter - Release' Hypothesis'*

*Channel Gating*: Landgren and Neil (1951), reported a stimulation of the carotid sinus nerve activity in response to stagnation of blood flow due to a fall in blood pressure by producing haemorrhage in cats. This was attributed by them, to the accumulation of some metabolite or by-product of cellular activity which brought about depolarization of nerve endings under these circumstances. This view led to the genesis of the transmitter-release hypothesis to explain the mechanism of impulse initiation at chemoreceptors. According to this, it is now believed that in the presence of hypoxia, the glomus type I cells are depolarized leading to voltage-gated calcium entry into them (Buckler & Vaughan-Jones 1994) and secretion of neurotransmitters, by exocytosis, which diffuse to the nerve terminal and depolarizes its membrane (Montoro et al. 1996). Although unstated by its proponents, the transmitter-release theory, inadvertently, makes the following two assumptions:

(i) that the transmitter substances would continue to be synthesized and the release processes continue to function till long after the animal is dead.(Anand &Paintal 2000) –this is based on the observation that, a stimulation of aortic chemo- receptor activity in response to ventilating the cats with pure $N_2$continues till long after a circulatory arrest has been produced in the animals (Paintal 1967, *see also* Joels & Neil 1963)

(ii) transmitter must act on the generator region of the sensory terminal and the impulse propagated centrally from the regenerative region.

Though, the first assumption is highly unlikely, given the energy requirements of the subcellular processes leading to transmitter release - the second is just as untenable because the usual transmitter substances including putative transmitters and especially acetylcholine are unlikely to act on the generator region. This has been supported by Hamill and McBride (1996).

*Biophysical Events Upstream to Transmitter Release*

There are various views on how the voltage-gated channels function. These are based on studies of cultured type I cells. These have been made possible by a number of technical advances that have occurred, such as whole cell-clamp and patch-clamp recordings, whereby a membrane patch can be stimulated and the current-response studied.

(i) One view, is that of Buckler (1999), who proposed that the release is not caused through the inhibition of the usual calcium activated or delayed $k^+$ channels. These channels, according to him are not inhibited by channel blockers such as TEA (tetra ethyl ammonium) and 4-AP (4-aminopyridine) but can be blocked by $Ba^{+2}$ (Buckler 1999). According to Donnelly (1999), if these channels do indeed represent the initial step in hypoxia transduction cascade, then it would be expected that $K^+$ channel blocking agents would mimic the hypoxia response leading to glomus cell secretion of the transmitter substance and increased nerve activity. Blockers such as TEA, 4-AP, however, have been without notable effect on the afferent response in whole animals and thus a role for oxygen-sensitive $K^+$ channels in hypoxia transduction is not firmly established (Donnelly 1999).

(ii) *Role of Heme proteins*: Based on *in vitro* studies on the rat carotid body under the influence of carbon monoxide, Lahiri has proposed that a certain variety of heme proteins that are able to sense the level of tissue oxygen tension, as determined by their redox state,

could be involved in opening up of membrane channels for transmitter release (Lahiri & Acker 1999).

(iii) Based on *in vitro* studies, Prabhakar (1999) hypothesized that during normoxia the chemosensory discharges of the carotid sinus nerve are inhibited by the production of nitric oxide (NO) and carbon monoxide (CO) within the sensory cells. During hypoxia, production of NO is decreased by inhibition of the enzyme, nitric oxide synthase (responsible for NO production) and that of CO, by the inhibition of the enzyme heme oxygenase-2. This results in reducing the inhibitory influence of NO and CO leading to an increased transduction activity. However, NO has been postulated as a transmitter (or else as a modulator) in those nerves of the autonomic nervous system where transmission is clearly by transmitter release but definitely not by acetylcholine or by adrenaline (*see* Moncada 1991).

*Possible Transmitters*

A number of neuroactive agents that have been proposed from time to time. These are presumed to be localized in type I cells and are known to have a transmitter-like function across certain synaptic junctions. Some of them are- acetylcholine, dopamine, substance P(SP), metenkephalin, atrial natriuretic peptide (ANP) and endothelin and more recently, nitric oxide (NO). Acetylcholine was the first to emerge as a likely candidate for transmission and has been seriously investigated by Eyzaguirre (Eyzaguirre & Zapata 1968). In a recent review, Eyzaguirre, the main protagonist of the transmitter hypothesis (Eyzaguirre & Abudara 1999) acknowledged that the main problem with it, in general and with acetylcholine as a candidate in particular, was that specific blockers of acetylcholine could modify the response of chemoreceptors to the stimulus being tested (i.e. hypoxia) but not block it completely. Thus, TEA can block the stimulation of chemoreceptors in response to injected acetylcholine but not to the stimulation produced by hypoxia (Donnelly 1995). However, *in vitro* studies that demonstrate release of acetylcholine by glomus cells during hypoxia continue to be pursued. These have succeeded in showing that additional cholinergic blockers such as mecamylamine and atropine, only depress the chemoreceptor response to hypoxia but do not block it (Fitzgerald et al. 1997).

Dopamine does not exhibit a dose response relationship to sensory activity of chemoreceptors - in smaller doses (less than 10μg $kg^{-1}$) it produces an inhibitory effect on stimulation by hypoxia and in higher doses (10-50 μg $kg^{-1}$) it excites the receptors. Substance P significantly depresses the effects of hypoxia *in vitro* whereas intracarotid injections produce stimulation. However, these neurotransmitter candidates are now considered by their proponents as modulators of the excitatory responses evoked either by acetylcholine, hypoxia or other chemical excitants (Zapata et al. 2000).

Finally, Eyzaguirre and Abudara (1999) have suggested recently that multiple agents could be acting as synaptic transmitters and to demonstrate a block of the stimulation of chemoreceptors by hypoxia, a cocktail of blockers would be required! It may be noted that, in none of the above studies carbon dioxide, as a stimulus, has found a place as yet, in the scheme of things describing channel gating leading to transmitter release.

*'Mechanical-Deformation Hypothesis'*

Therefore, we need to consider that the sensory endings of chemoreceptors are mechano-sensitive and that the generator region of the nerve endings is stimulated by mechanical deformation caused by the alteration in the shape/size of the type II cells brought about by hypoxia. This view was proposed by Paintal (1967) and subsequently substantiated by further evidence (Anand & Paintal 1990,1991). Such a mechanism is known to exist at several other sensory cell types. Further, examples of a stimulation of carotid and aortic chemoreceptors by mechanical stimuli such as, by sharp increases in vascular pressure and compression of the area in which they are located, have been described recently (Anand & Paintal 2000). One such example is illustrated in figure 2. Some of the well known forms of mechanical stimulation at the cellular level are cell stretch and compression, osmotic swelling, fluid shear stress (Hamill & McBride 1996).

In summary, it is suggested that hypoxia may produce loss of intracellular fluid leading to a shrinkage of cells (such as type II). Possibly this is

similar to surrounding the carotid body with hyperosmotic solutions which depolarizes glomus cells leading to a greater discharge of impulses *in vitro* (Gallego et al. 1979) and *in situ* (Trzebski et al 1978). The likely intervening steps suggested by Anand and Paintal (2000) are depicted in the flow diagram of figure 3. It is possible that $CO_2$ ($HCO_3^+$), acts on the regenerative region of the nerve endings in much the same way, as drugs do, to produce a stimulation of chemoreceptors (Paintal 1964). That the response to drugs must adapt to the stimulus applied, must account for the stimulation by $CO_2$, being of a dynamic rather than of a sustained nature (Hanson et al. 1979). In a more recent study of the stimulation of ventilation by $CO_2$, in humans, Pederson et al.1999 differentiated two kinds of responses–a fast response (from peripheral chemoreceptors) and a slower response from the central (brain stem) chemoreceptors .

## Role under Physiological Conditions

The chemoreceptors without exception have been considered as receptors that are stimulated under hypoxic circumstances which normally are not encountered during physiological conditions at sea level. Under fetal conditions of hypoxia, the arterial chemoreceptors are quiescent–being activated ('switched on') only after birth. In fetal lambs a stimulation of their activity can be induced by increasing the level of hypoxia, (Blanco et al. 1984) or by reducing oxygen saturation (Boekkooi et al. 1992), via the placental circulation. Stimulating them by injecting cyanide via the fetal left atrium produces some bradycardia, a delayed hypertension and a few gasps, reflexely (Itskovitz & Rudolph 1987). However, it is not quite certain whether the arterial chemoreceptors are crucial to the fetus' survival during prolonged hypoxia since Jansen and Chernick (1974) do not rule out the possible role of the central nervous system in the cardiorespiratory responses seen during episodes of severe hypoxia. Arterial hypoxia may be encountered only during certain disease states such as *chronic obstructive lung disease* where the arterial $p_{O2}$ is below 55 mmHg (Bradley et al. 1979). Thus, one has to look further than hypoxia for their role in physiology. One such mechanism, as has been discussed above, is hypotension. In cats, a fall in the mean systemic blood pressure even by

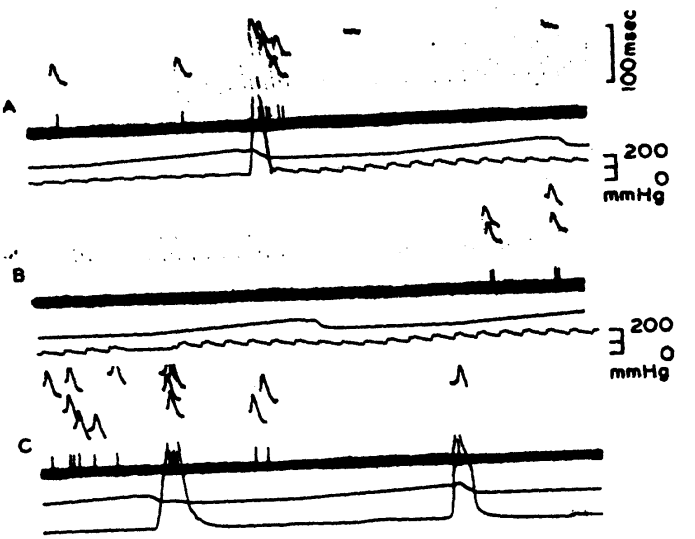


**Figure 2** Effect of intracarotid pressure pulses on a carotid chemoreceptor. The pressure pulses were produced by injecting slugs of saline into the carotid artery (last trace) in panels A & C which show a considerable rise in pressure (calibration on the right ; absent in panel C). The topmost series of expanded vertical sweeps show the relatively high frequency of discharge produced by the pressure pulses (calibration for the sweeps on the right of panel A). (*after* Anand & Paintal 2000).

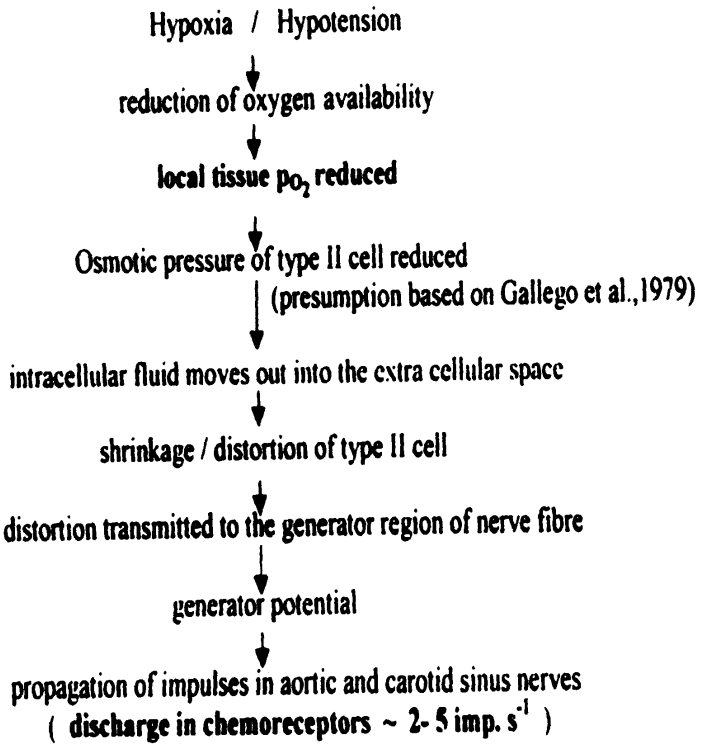


**Figure 3** Schematic diagram of possible events that produce mechanical deformation of the chemosensory nerve ending in the presence of reduced oxygen availability leading to transduction of nerve impulses.

10-20 mmHg (at both normo- [figure 1] and hypotensive levels [figure 2], Anand and Paintal 1988) is sufficient to produce a noteworthy stimulation of aortic chemoreceptors with very short latencies (figures 3 & 4). Furthermore, a fall in the mean systemic blood pressure by 35 mmHg increases their activity from near silence to 3 impulses $sec^{1}$ and which is about one-third that of maximally produced stimulation i.e. with circulatory arrest (Anand & Paintal 1988). These findings are consistent with earlier findings of Lee et al.1964, Paintal 1967, Lahiri et al.1980b on aortic chemoreceptors, but at variance with those on the carotid chemoreceptors (Biscoe et al. 1970, Lahiri et al. 1980b). The lack of stimulation of carotid chemoreceptors by a fall in the systemic blood pressure within the physiological range was attributed by Paintal (1968), to the influence of the external environment during experimentation because atmospheric oxygen diffuses into the carotid body (which is stripped of its connective tissue for exposing the carotid sinus nerve for electrical recording) and offsets the stimulus of a decrease in arterial $p_{O2}$. On the other hand a notable stimulation of aortic chemoreceptors, whose external environment inside the chest is kept intact, is seen in response to hypotension. Additionally, stimulation of chemoreceptors by hypotension i.e. in the absence of an unchanged arterial oxygen tension (Anand & Paintal 1988), suggests that the stimulus is not the arterial $p_{O2}$ but reduced availability of oxygen, at the receptor site, which in this case is due to low blood flow rate. Physiologically, a fall in blood pressure encountered in postural hypotension (due to a fall in cardiac output) would stimulate chemoreceptors. This would reflexely raise the blood pressure and prevent any adverse effect such as fainting etc., from occurring. This would be in addition to a similar effect obtained through the arterial baroreceptors whose activity would have fallen during hypotension.

*Role of Sympathetic Outflow*

Sympathetic outflow to the aortic bodies was demonstrated to exert an excitatory influence on chemoreceptor activity. Its action, attributed to glomeral vasoconstriction, leads to a reduction in the glomeral blood flow and thereby, of oxygen availability (Anand 1996). As the level of sympathetic outflow increases during hypoxia and hypotension (and during hypercapnia) the activity of chemoreceptors, in the presence of these stimuli represents their response not only to them but also to the stimulation provided by vasoconstriction (Anand & Paintal 1988, Anand 1996). An important point that emerged from this study was, that the small amount of chemoreceptor activity seen during normoxia represents not only the effect of the arterial $p_{O2}$ but also the effect of the existing level of sympathetic outflow. In view of the fact that aortic chemoreceptors raise blood pressure reflexely, this finding has some important implications. In people with a tendency to increased sympathetic activity e.g. in those with essential hypertension, the aortic chemoreceptors may be more active and contribute to the higher levels of blood pressure in them (Tafil & Trzebski 1984). Though an increase in the cervical sympathetic outflow and in carotid chemoreceptor activity has been recorded in response to exercise in the anaesthetized cat (Biscoe & Purves 1967) yet these authors do not find this as sufficient evidence to attribute the cardiorespiratory changes seen during exercise in humans, entirely to stimulation of chemoreceptors in this indirect manner. Other evidence suggests the additional involvement of cortical and hypothalamic mechanisms (Krogh & Lindhard 1913).

## Conclusions

A few novel points emerge from the above account. There is still no evidence to substantiate the view that the mechanism of transduction of nerve impulses is by release of transmitters. Ion-gated channels and co-messengers described thus far, may be an 'epiphenomenon' occurring during reduced oxygen availability. Hypotension is the only stimulus that chemoreceptors are exposed to physiologically and sympathetic vasoconstrictor influences determine the level of the stimulus to the chemoreceptors at any given arterial oxygen tension and blood pressure value.

Future work demonstrating transduction of impulses by mechanical deformation should aim at determining (i) whether hypoxia indeed leads to a shrinkage of sensory cells (ii) and whether these structural changes increase as oxygen falls, or, are more cells or nerve endings recruited. (iii) Finally, and most importantly, a reversal of these effects when the stimulus ceases has to be demonstrated.

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