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Peripheral arterial chemoreceptors and the evolution of the carotid body

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Abstract

There has been a reduction in the distribution of peripheral respiratory O_2 chemoreceptors from multiple, dispersed sites in fish and amphibia to a single dominant receptor site in birds and mammals. In the process, the cells in the fish gill associated with O_2 chemosensing (5-HT containing neuroepithelial cells often found in association with ACh/catecholamine (CA) containing cells) are replaced by the glomus cells of the mammalian carotid body (which contain multiple putative neurotransmitter substances, including 5-HT, CA and ACh, all within the same cells), although this difference may be more superficial than first appears. While still highly speculative, these trends would appear to be correlated with the transition from aquatic respiration and bimodal breathing, and from animals with intra-cardiac shunts (two situations where the ability to sense O_2 at multiple sites would be an advantage), to strictly air breathing in animals with no intra-cardiac shunts. It is also tempting to speculate that while the basic O_2-sensing mechanism is the same for all receptor cells, the receptor groups in fish have evolved in such a way to make the responses of some more sensitive to changes in O_2 delivery than others. The net result is that those receptors associated with the first gill arch of fish (the third branchial arch) become the carotid body in higher vertebrates associated with the regulation of ventilation and ensuring oxygen supply to the gas exchange surface. Those receptors associated with the second gill arch (fourth branchial arch) become the aortic bodies capable of sensing changes in oxygen content of the blood and primarily involved in regulating oxygen transport capacity through erythropoiesis and changes in blood volume.

Keywords: Phylogenetic trends; Vertebrates; O_2-sensitive chemoreceptors; Carotid body; Aortic body; Gill

1. Introduction

The phylogeny of O_2 and CO_2/pH chemoreception is a topic that has received much attention over the past few years giving rise to several reviews, each with its own unique focus (see for instance: Gilmour, 2001; Perry and Gilmour, 2002; Milsom, 1998, 2002; Burleson and Milsom, 2003). Given this, the brief review presented here extracts key information with a focus on two specific questions that we feel are relevant to the topic of this special issue of *Respiratory Physiology & Neurobiology*. Specifically, the present review focuses on the trends seen in O_2-chemosensing cells associated with the carotid artery and on the possible origins of their unique role in cardiorespiratory control.

While the phylogeny of the carotid arteries is well established, the phylogeny of the carotid body is not. In the most primitive vertebrates, blood leaving the heart first enters an unpaired ventral aorta. The ventral aorta immediately gives rise to a series of aortic arches, which pass dorsally within the branchial arches between the pharyngeal slits, to form a paired dorsal aorta. Arising from the anterior end of the dorsal aorta are the internal carotid arteries which provides blood to the head and brain. The external carotid arteries which carry blood to the ventral region of the head generally arise from the anterior end of the ventral aorta although, in some cases, they arise from the efferent branchial arteries of the third embryonic branchial arch. Beginning with the amphibians, the short section of ventral aorta between embryonic branchial arches III and IV (gill arches 1 and 2) becomes the common carotid artery which feeds the external carotids, arising from the anterior ventral aorta, and the internal carotids, arising from the anterior dorsal aorta and the third aortic arch. In most vertebrates (but not all, see below), the carotid body is located at the junction between the internal and external carotid arteries. In fish, however, the third aortic arch lies between the internal and external carotid arteries and it is along this route that the origins of the carotid body should lie. Of key interest are the similarities and differences that are found in O_2-sensing cells in these locations (first gill arch and its derivative, the carotid bifurcation) and the reflexes they give rise to.

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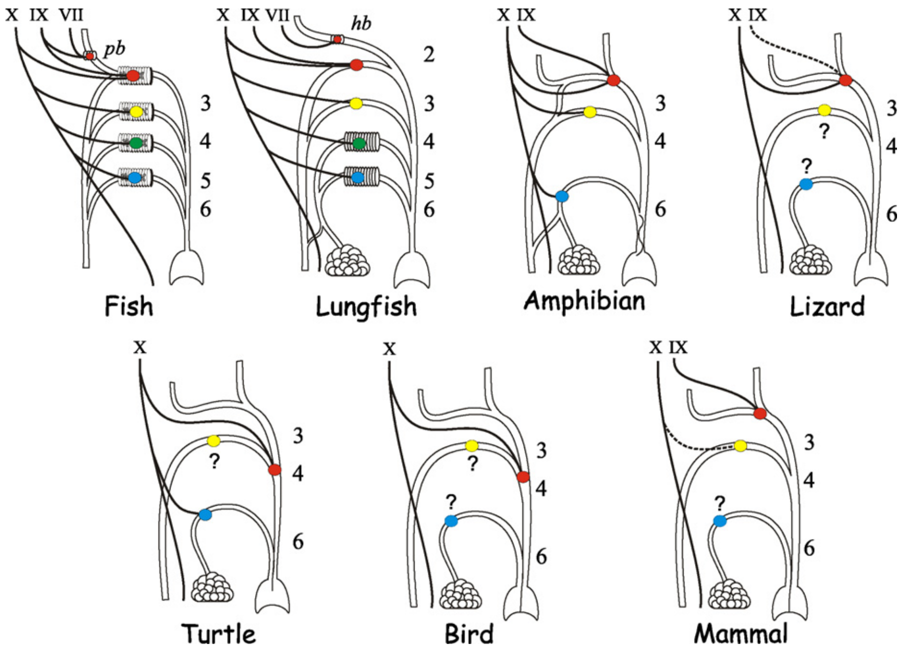

Fig. 1. Schematic diagram to illustrate the distribution of O_2-sensitive chemoreceptors in different vertebrate groups. VII, IX and X refer to cranial nerves (facial, glossopharyngeal and vagus nerves) while 2–6 refer to arteries supplying the respective embryonic gill arches. While O_2 chemoreceptors are found in the aortic bodies of mammals, they do not appear to serve a respiratory role. See text for further details (from Burleson and Milsom, 2003). pb, pseudobranch; hb, hemibranch.

2. Location and innervation of peripheral arterial O_2 chemoreceptors

Studies over the past five decades provide fairly strong evidence that oxygen-sensitive chemoreceptors in fish can be found all along the respiratory passages. They have been reported within the walls of the orobranchial cavity innervated by cranial nerves V and VII (Butler et al., 1977; Smatresk, 1990). They also occur in the spiracle and pseudobranch in species that have such structures, innervated by cranial nerves VII and IX (Burleson et al., 1992). Finally, they can be found on all gills in fish, innervated by cranial nerves IX and X (Fig. 1).

The exact distribution of these receptors is highly variable from species to species, however, as are their roles in various physiological processes. Hypoxia produces a reflex bradycardia in fish and the receptors associated with this are restricted to the first gill arch in many species (trout, cod and traira; Smith and Jones, 1978, 1982; Fritsche and Nilsson, 1989; Sundin et al., 1998a,b), but can be found throughout the first 3 pairs of gill arches in others (catfish; Burleson and Smatresk, 1990a) and within the orobranchial cavity in the elasmobranch fishes (dogfish; Butler et al., 1977; Taylor et al., 1977). The hypoxic ventilatory response, on the other hand, only arises from receptors confined to the gill arches in a few species (catfish; Burleson and Smatresk, 1990b); in many fishes, total gill denervation fails to eliminate the hypoxic ventilatory response (sea raven, tench, tambaqui; Saunders and Sutterlin, 1971; Sundin et al., 1998b) and the remaining receptors appear to occur at extrabranchial sites including the orobranchial cavity (tambaqui, Milsom et al., 2002).

Air breathing has arisen in fishes many times utilizing various surfaces of the alimentary canal including parts of the buccal and pharyngeal cavities. The most derived forms make use of either air breathing organs or true lungs (Gans, 1970). Oxygen-sensitive chemoreceptors in these fishes now regulate not only changes in heart rate and gill ventilation but also ventilation of the air breathing organs. The sites and innervation of the oxygen-sensitive chemoreceptors that stimulate gill breathing and air breathing have not been studied extensively. In the Actinopterygian fishes, the gar and bowfin, they are found diffusely distributed throughout the gills and pseudobranch innervated by cranial nerves VII, IX and X (McKenzie et al., 1991; Smatresk et al., 1986; Smatresk, 1988; Coolidge et al., 2007). In the Dipnoan lungfishes, they are also distributed throughout the anterior hemibranch and all gill arches innervated by cranial nerves VII, IX and X (Fig. 1) although data suggest that ventilatory reflexes arise principally, but not exclusively from receptors in the hemibranch and the anterior two (filament free) arches (Lahiri et al., 1970).

In amphibians, the homologues of all these sites, except perhaps the orobranchial cavity, remain active as O_2-sensing sites. Amphibian tadpoles begin life as skin and gill breathers and during late metamorphosis both gills and lungs are present. The first extant gill arch (embryonic branchial arch 3) subsequently becomes the carotid labyrinth and is innervated by cranial nerve IX. Studies indicate that the initial rapid response to environmental hypoxia arises exclusively from this arch while the subsequent slow component of the hypoxic ventilatory response arises from receptors at other sites (Jia and Burggren, 1997). In amphibians, the aortic arch is a homologue of the fourth embryonic gill arch innervated by the Xth cranial nerve and the pulmocutaneous artery is a homologue of the sixth embryonic gill arch innervated by the Xth cranial nerve. In adults, all appear to contain oxygen chemoreceptors that participate in respiratory reflexes (Fig. 1) (Ishii et al., 1985a,b; Van Vliet and West, 1987; West et al., 1992).

In the majority of lizards, indirect evidence suggests that O_2 receptors are located where the internal carotid artery arises from the common carotid artery innervated by the superior laryngeal branch of the vagus nerve and perhaps also from the glossopharyngeal nerve (Fig. 1) (see Milsom, 1990; Smatresk, 1990 for reviews). In birds and turtles, on the other hand, chemoreceptive tissue is not present at the extant carotid bifurcation but during embryological development the aortic arches retreat backwards and the carotid bifurcation remains close to the heart. The external carotids then atrophy and the internal carotids (now called common carotids) divide, secondarily, in the head region (see Jones and Milsom, 1998 for review). As a result the site homologous to the carotid bifurcation in amphibia and mammals is now part of the aortic arch. In birds and turtles, the largest aggregations of chemoreceptive tissue are found in the central cardiovascular area and are innervated by one or more vagal branches from the nodose ganglion (Fig. 1) (Abdel-Magied and King, 1978; Ishii et al., 1985a). Given the weight of the evidence, these receptors are believed to be homologous to the carotid chemoreceptors of other vertebrates.

In mammals the carotid bodies are situated at the bifurcations of the common carotid arteries into their internal and external branches. Afferent nerve fibres arising from these structures travel in the sinus nerve, a branch of the glossopharyngeal nerve (Fig. 1). The aortic bodies in mammals, on the other hand, are located in the region of the aortic arch and the roots of the major arteries of the thorax. Their afferent fibres run in the aortic nerve, a branch of the vagus nerve (Fig. 1). They appear to make little contribution to the resting ventilatory drive in eucapnic normoxia and may not even contribute to the hypoxic ventilatory response in many species. It would appear that they participate primarily in cardiovascular reflexes in this group (see Fitzgerald and Lahiri, 1986 for review). Glomus tissue which may be homologous to the aortic chemoreceptors of mammals has also been described within the aortic walls of birds (Nye, 1984). Electrophysiological studies on aortic bodies of chickens have shown that isolated epithelioid cells of the chicken thoracic aorta release 5-HT following depolarizing stimuli and express voltage activated K^+ currents that are inhibited by hypoxia, similar to carotid body glomus cells (Ito et al., 1999). Oxygen chemoreceptors have also been reported to occur on the pulmonary arteries of turtles, birds and mammals but only those in turtles have been reported to give rise to ventilatory reflexes (Ishii et al., 1985a,b).

This information is summarized in Fig. 1 and inspection of this figure reveals two trends quite clearly. The first is that all O_2 chemoreceptors involved in respiratory control are situated peripherally; there is no strong data yet to argue for the presence of central O_2 chemoreceptors involved in respiration. The second is that there has been a trend to reduce the distribution of O_2 chemoreceptors from multiple, dispersed sites in fish and amphibia towards a single dominant receptor site in birds and mammals. While still highly speculative, this latter trend would appear to be correlated with two events. The first is the transition from aquatic respiration and bimodal breathing (where the ability to sense O_2 at multiple sites would be an advantage) to strictly air breathing in animals. There is much less and highly variable O_2 in water compared to air. Correlated with this, ablation or denervation of the carotid bodies in mammals has little effect on blood gases whereas gill denervation drastically reduces blood O_2 levels in catfish (Burleson and Smatresk, 1990b) and Amia (McKenzie et al., 1991). The second is the transition from animals with intra-cardiac shunts (another situation where the ability to sense O_2 at multiple sites would be an advantage) to animals with no intra-cardiac shunts. In amphibia and reptiles with well-developed intra-cardiac shunts, increases in arterial oxygen transport can be achieved by both reducing the degree of cardiac shunt as well as increasing ventilation. Having multiple O_2 receptors at appropriate sites may allow these species to make appropriate changes that most effectively increase oxygen transport under different conditions (see below). In birds and mammals, respiratory control is much less flexible (one exchange site which must receive the total cardiac output) and it would appear that under these conditions efficient control can be achieved with chemoreceptive information from a single source. Thus, oxygen receptors associated with homologous structures to the first gill arch (third branchial arch) of fish appear to become the primary respiratory O_2 chemoreceptor while those associated with structures homologous to the remaining gill arches take on a secondary role and/or become more involved in cardiovascular reflexes (see below).

3. Chemosensing cells and mechanism of transduction

The tissue involved in O_2 chemoreception in mammals has a characteristic association of glomus cells (also known as chief cells or Type I cells), sustentacular cells (also known as Type II cells) and nerve terminals. The glomus cell complex is characterized by both presynaptic and postsynaptic cytoplasmic vesicles containing a profusion of different transmitters and neuromodulators. Neurotransmitter co-storage is common and electrical coupling via gap junctions has been demonstrated as well. It is believed that this tissue is derived from embryonic, neuroendocrine programmed cells. These cells are also sensitive to multiple stimuli in the blood ranging from changes in O_2 to changes in CO_2, $[H^+]$, $[K^+]$, [glucose], other osmolytes, temperature and possibly blood pressure (see reviews by Kumar and Bin Jaliah, this issue; Buckler, this issue; López-López and Pérez-Garcia, this issue; Peers and Wyatt, this issue). Several hypotheses have arisen from recent research to explain chemotransduction in the carotid body. These are the topics of the other reviews contained within this special issue. One thing of note is that most researchers consider ACh and ATP to function as the major neurotransmitters or modulators of the glomus cells with the catecholamines, substance P, 5-HT, and the opiates playing more of a role in modulating the effects of other substances (see Table 1 and reviews in this issue).

Much less is known about the tissue associated with O_2 chemoreception in other vertebrates. There have, however, been a series of excellent studies conducted recently on the putative O_2-sensing cells within the gills of fish that raise intriguing questions about the phylogeny of the O_2-chemosensing complex. To

Table 1
Neurochemicals identified in O_2-sensing cells from various taxa

Mammals
Serotonin
Dopamine
Norepinephrine
Acetylcholine
Epinephrine
Substance-P
Enkephalins
Nitric oxide
Neuron-specific enolase
Tyrosine hydroxylase
Birds
Serotonin
Substance-P
Neuron-specific enolase
Tyrosine hydroxylase
Reptiles
Serotonin
Enkephalins
Neuron-specific enolase
Tyrosine hydroxylase
Amphibians
Serotonin
Enkephalins
Neuron-specific enolase
Tyrosine hydroxylase
Fish
Serotonin
Enkephalins
Neuron-specific enolase
Tyrosine hydroxylase

date the primary chemoreceptor cells within the gills of fish have been postulated to be neuroepithelial cells (NECs) identified by the presence of 5-HT in dense-cored vesicles (Dunel-Erb et al., 1982; Donald, 1984; Laurent, 1984; Donald, 1987; Zaccone et al., 1992; Goniakowska-Witalinska et al., 1995; Jonz and Nurse, 2003). Innervated NECs have been located at the filament tips in the gills of all fish in a prime location to sense changes in aquatic O_2 levels (P_wO_2) (Sundin et al., 1998a; Jonz and Nurse, 2003). This is in agreement with physiological data, indicating that all fish studied to date respond to aquatic hypoxia (Randall and Smith, 1967; Cameron and Wohlschlag, 1969; Cameron and Davis, 1970; Saunders and Sutterlin, 1971; Holeton, 1971; Wood et al., 1979; Smith and Jones, 1978; Smatresk et al., 1986; Burleson and Smatresk, 1990a; McKenzie et al., 1991; Burleson and Milsom, 1995a; Sundin et al., 1998b, 2000; Milsom et al., 2002). There are also NECs present surrounding the efferent filamental artery in a prime location to monitor arterial O_2 levels (P_aO_2), but these are species-specific and correlated with the ability of fish to respond to internal (arterial) hypoxaemia (see below). Fish gill NECs have been isolated and shown to respond to acute hypoxia with inhibition of plasmalemma K^+ channels, leading to membrane depolarization just as do the glomus cells of mammals (Jonz and Fearon, 2004). Finally, tyrosine hydroxylase (indicative of catecholamine secretion) and neuron-specific enolase (indicating that NECs like glomus cells are derived from the neural crest) have also been found in fish NECs (Burleson et al., 2006).

Supporting this parallel between the glomus cells of mammals and the NECs within the gills of fish are two observations. The first is that the main role of 5-HT in chemosensing in mammalian glomus cells is one of modulation (Zhang and Fearon, 2003). The second is that exogenous systemic application of 5-HT produced only a modest excitation of O_2 chemoreceptors in single fibre recordings from the gills of rainbow trout (Burleson and Milsom, 1995a) although 5-HT did cause a significant rise in ventilation amplitude in intact fish (Fritsche et al., 1992; Burleson and Milsom, 1995b). The neurotransmitter producing the most robust response with exogenous application was ACh acting via nicotinic receptors (Burleson and Milsom, 1995a). Most recently, catecholamines (CA) and ACh have also been demonstrated to be abundant in the gill filaments of fish, usually co-localized to the same cells (Coolidge and Milsom, unpublished). 5-HT, however, was rarely co-localized with acetylcholine and never with catecholamines. Often however, 5-HT containing cells and ACh/CA containing cells occurred as neighbors (Coolidge and Milsom, unpublished). While these results are not inconsistent with the hypothesis that NECs are the putative O_2 chemoreceptors in the gills, they raise the possibility that 5-HT containing NECs may participate in O_2 chemoreception by modulating the release of acetylcholine and/or catecholamines from neighboring cells, which may or may not themselves be chemoreceptive. Certainly 5-HT appears to be abundant in rodent carotid glomus cells and may play an important modulatory role in responses to acute hypoxia as well as in responses to intermittent hypoxic stimuli (Peng et al., 2006; Powell, this issue; Prabhakar et al., this issue; Zhang and Fearon, 2003).

The observation that the Type I glomus cells of the mammalian carotid body contain multiple putative neurotransmitter substances, including 5-HT, CA and ACh, within the same cells, while 5-HT and ACh/CA appear to occur in separate cells within the fish gill, raises questions about the possible evolution of the mammalian glomus cell complex from a fish gill NEC complex. While there is still too little data to speculate about how such a transformation may have come about, the observation that chemoreceptor cells within the mammalian carotid body exhibit a continuous gradation in a number of immunocytochemical, neurochemical and electrophysiological properties (Gonzalez et al., 1995) may indicate that similarities between the groups may be greater than differences.

4. Orientation: hypoxia versus hypoxaemia

Many fish, air-breathing fishes and amphibian larvae are able to distinguish between environmental hypoxia and internal hypoxaemia. The ability to sense and respond quickly to changes in environmental O_2 might serve as a first line of response that serves to minimize the effects of these changes on systemic P_{O_2}. Changes in systemic P_{O_2}, on the other hand, would either serve to initiate a second line of response or, the first line of response to changes in metabolic demands independent of changes in environmental O_2 availability.

Based on reflex studies, the hypoxic bradycardia exhibited by most teleost fish appears to be triggered by activation of externally oriented receptors that monitor aquatic O_2 levels. These receptors are found largely on the first gill arch but have been reported on other gill arches in some species (see Burleson et al., 1992). Not all fish follow this pattern, however. In the gar and the tambaqui they appear to be sensitive to both internal and external changes in P_{O_2} (Smatresk et al., 1986; Sundin et al., 2000) while in the neotropical fish, the traira, they appear to only monitor the P_{O_2} of the blood (Sundin et al., 1998b). By contrast, the O_2-sensitive receptors instrumental in producing the increases in ventilation frequency and amplitude in most teleost fish appear to monitor both the blood and water (Randall and Smith, 1967; Cameron and Wohlschlag, 1969; Cameron and Davis, 1970; Saunders and Sutterlin, 1971; Holeton, 1971; Wood et al., 1979; Smith and Jones, 1978; Smatresk, 1986; Burleson and Smatresk, 1990a; McKenzie et al., 1991; Burleson and Milsom, 1995a; Sundin et al., 1998b, 2000; Milsom et al., 2002). Consistent with this, electrophysiological studies on both tuna and trout have noted afferent activity arising from fibers that responded only, or preferentially to changes in external (water) O_2 stimulus levels and others that responded only, or preferentially to changes in internal (perfusate/blood) O_2 stimulus levels (Milsom and Brill, 1986; Burleson and Milsom, 1995a). In these studies, some fibres were found that were sensitive to changes in O_2 partial pressure in both the water bathing the gills and the fluid perfusing the gills.

Many air-breathing fishes and amphibian larvae are also able to distinguish between environmental hypoxia and internal hypoxaemia. NaCN has been shown to be a potent stimulus to O_2 chemoreceptors and either aquatic hypoxia or injection of NaCN into the water flowing over the gills has been shown to stimulate air-breathing in both facultative (bowfin, gar and *Ancistrus*) (Johansen et al., 1970; Graham and Baird, 1982; McKenzie et al., 1991; Randall et al., 1981; Smatresk et al., 1986) and some obligate (Australian lungfish) air-breathers (Johansen et al., 1967) as well as in the neotenous gill-bearing axolotl, Ambystoma (McKenzie and Taylor, 1996). More advanced obligate air-breathers have very reduced gills and no longer appear to respond to changes in aquatic P_{O_2} (*Protopterus* and *Lepidosiren*; Johansen and Lenfant, 1968; Sanchez et al., 2000). The effect of such manipulations on gill ventilation in facultative air-breathers is less consistent leading to an inhibition of gill ventilation in gar and the Australian lungfish (Johansen et al., 1967; Smatresk et al., 1986) but a stimulation of gill ventilation in the catfish, bowfin, reedfish, gar and the axolotl (Johansen et al., 1970; Smatresk and Cameron, 1982; McKenzie and Taylor, 1996). It is not clear whether this simply reflects the levels of aquatic hypoxia employed in these studies since it has been shown in amphibian tadpoles that mild hypoxia stimulated gill ventilation but more severe hypoxia inhibited gill ventilation and stimulated lung ventilation (West and Burggren, 1983). Injection of NaCN into the blood stream (dorsal aorta) also stimulates air breathing in the African lungfish, the gar, and the axolotl but fails to do so in the bowfin. It did, however, stimulate gill ventilation in all of the facultative air-breathers (gar and bowfin and axolotl) (Graham and Baird, 1982; McKenzie and Taylor, 1996; McKenzie et al., 1991; Smatresk et al., 1986).

O_2-sensitive chemoreceptors in exclusively air-breathing species all appear to be designed to monitor only the internal environment.

5. Stimulus specificity

The linkage between changes in arterial P_aO_2 and chemosensory discharge in chemosensing cells has remained an elusive one. Several hypotheses exist, which are not mutually exclusive, and which are thoroughly outlined in other chapters in this issue (Wyatt and Evans, this issue; Dinger et al., this issue; Shirahata et al., this issue; Zapata, this issue; Lahiri et al., this issue; Ortega-Sáenz et al., this issue). What has received less attention is the correlation between hypoxic ventilatory responses, chemosensory discharge and the oxygen content or saturation of the blood.

Many vertebrates appear able to distinguish between changes in the O_2 saturation of the blood and changes in arterial O_2 partial pressure. While the O_2 saturation of the blood is normally tightly linked to the arterial O_2 partial pressure, this is not always the case. Teleologically, it follows that the most appropriate response to a change in O_2 partial pressure is to increase ventilation (increase P_{O_2} regardless of O_2 content) while the most appropriate response to a change in O_2 content is to increase Hct or blood volume (increase O_2 content regardless of O_2 partial pressure).

Many vertebrates show a much stronger correlation between the threshold for the hypoxic ventilatory response and O_2 saturation than with P_aO_2. Thus, in fish, ventilation rate varies inversely with blood oxygen content, independently of partial pressure, indicating that arterial receptors respond to the rate of delivery of oxygen to the receptor site (Randall, 1982; Smith and Jones, 1982) and throughout the air-breathing vertebrates there are strong indications that this is also the case. It has been argued that in animals where adaptive changes occur in the ability of hemoglobin to bind oxygen, O_2 saturation would be a better indicator of the O_2 homeostasis of arterial blood than P_aO_2 (Wood, 1984). Thus, in turtles and hibernating ground squirrels there are reductions in the P_aO_2 threshold of the hypoxic ventilatory response accompanying the temperature induced increase in the ability of hemoglobin to bind oxygen as body temperature decreases (Glass et al., 1983; Milsom et al., 1986). This is also the case with animals which exhibit an increase in hemoglobin–oxygen binding as a consequence of chronic exposure to hypoxia as occurs in animal burrows (Boggs and Birchard, 1983) or at altitude (Black and Tenney, 1980). In all cases, if the hypoxic ventilatory response is plotted against the % Hb saturation of arterial blood, ventilation begins to increase when saturation falls below 80–85% (Wood, 1984). It has been further shown that many species (ectotherm and endotherm) behaviourally reduce their body temperatures under hypoxic conditions, increasing oxyhemoglobin affinity such that levels of O_2 saturation are maintained despite the reduction in P_aO_2 (Hicks and Wood, 1985).

At present, only the aortic bodies of mammals have been shown to respond to changes in blood O_2 content per se, and although this does not seem to elicit any reflex ventilatory response, it does elicit reflex changes in blood volume and erythropoiesis (Lahiri et al., 1981). The responses of O_2 chemoreceptors to changes in O_2 saturation in most species of vertebrates have not been studied. Several hypotheses have arisen from recent research to explain chemotransduction in the carotid body. These hypotheses are not mutually exclusive. One group of researchers (López-Barneo et al., 1988) suggest that hypoxia leads to a reduction in the binding of O_2 to a heme protein receptor. One of the appeals of the hypothesis that a heme protein serves as the oxygen receptor in chemoreceptor cells is the possibility that this heme protein would share similar properties and be modulated in a similar fashion as the hemoglobin in any given species. If this were the case, binding properties of receptors would shift in parallel to the hemoglobin-binding properties with changes in temperature, organophosphates or other factors that alter the relationship between blood P_{O_2} and O_2 content or saturation and shift the position of the oxygen equilibrium curve of the blood (Boggs, 1995). This would maintain a tight coupling between receptor activation, blood oxygen saturation and ventilation despite the shift in the relationship between arterial O_2 content and P_{O_2}. In other words, even though the receptor only responds to changes in local P_{O_2}, the receptor binding properties might change in such a way under these conditions that receptor discharge only begins to increase significantly at the P_{O_2} at which hemoglobin begins to desaturate.

This same line of argument would also apply to P_{O_2}-sensitive chemoreceptors in the venous circulation as has been suggested to be the case for amphibians and turtles (Wang et al., 1997). In these animals two receptor populations with different reflex roles have been proposed to exist to explain why there are no ventilatory responses to reductions in blood oxygen content, whereas heart rate and pulmonary blood flow increase following reductions in blood oxygen carrying capacity due to anemia, inhalation of CO, or nitrite infusions (Wang et al., 1994, 1997; Wang and Hicks, 1996). O_2-sensitive chemoreceptors have been identified on the pulmocutaneous artery in amphibians as well as on the pulmonary artery in turtles (Van Vliet and West, 1992; Ishii et al., 1985a,b) and blood in these vessels is predominantly venous systemic blood although the exact composition depends on the level of left to right intra-cardiac shunt. This led to the suggestion that perhaps O_2-sensitive chemoreceptors on the pulmonary artery are responsible for cardiovascular control while the arterial chemoreceptors are responsible for ventilatory control (Wang et al., 1997). Recent experiments designed to test this hypothesis have been equivocal, however, and while not ruling out this possibility, indicate that there are receptors in both the carotid and pulmonary circulations that have over-riding effects on the cardiovascular system (Wang et al., 2004).

Another possible explanation of the observed correlations between cardiorespiratory changes and changes in arterial O_2 content that occur independent of changes in arterial P_{O_2} stems from the relationship between local tissue (and receptor cell) P_{O_2} and arterial P_{O_2}. P_{O_2} at the receptor site (which could be the cell surface or in the cytosol) is a function of mean capillary P_{O_2} which, in turn, is a function of blood oxygen affinity and the change in O_2 content due to local oxygen consumption as blood travels along the capillary (Eyzaguirre et al., 1983). The change in O_2 (which will in part determine the mean capillary P_{O_2}) will be a function of metabolic rate and the rate of oxygen delivery (blood flow) to the tissue. One of the appeals of this explanation is that it can account for the existence of distinct populations of receptor cells; aortic chemoreceptors that respond to changes in oxygen saturation (which well suits their primary role in regulating blood volume and oxygen carrying capacity) (Lahiri et al., 1981) and carotid chemoreceptors, which do not.

Whatever the mechanistic basis behind the apparent ability of some species to distinguish changes in arterial oxygen saturation independent of changes in oxygen partial pressure, the phylogenetic trend that appears is also a highly adaptive trend. In all fish, ventilation rate would appear to vary inversely with blood oxygen content, independently of partial pressure (Randall, 1982; Smith and Jones, 1982). In amphibians and reptiles, animals with intra-cardiac shunts, changes in shunt fraction appear to be tightly related to changes in O_2 content while changes in ventilation are less so. All air breathing vertebrates that undergo broad changes in body temperature show much tighter correlations between changes in O_2 delivery than in P_aO_2 per se. It is tempting to speculate that while the O_2-sensing mechanism may be the same for all receptor cells, their locations have evolved in such a way to make the responses of some more sensitive to changes in O_2 delivery than others. The net result is that those receptors associated with the first gill arch of fish (the third branchial arch) become the carotid body in higher vertebrates associated with the regulation of ventilation and ensuring oxygen supply to the gas exchange surface. Those receptors associated with the second gill arch (fourth branchial arch) become the aortic bodies, capable of sensing changes in oxygen content of the blood and primarily involved in regulating oxygen transport capacity through erythropoiesis and blood volume. If this turns out to be the case it would indicate that natural selection has acted on what might once have been a uniform population of O_2-sensing cells to produce two populations of sensors situated in different locations (carotid and aortic bodies), with different stimulus specificities (O_2 partial pressure versus O_2 content), acting to produce different reflex effects on O_2 delivery to the lungs (ventilation via stimulation of P_aO_2-sensitive carotid bodies) versus O_2 delivery to the tissues (blood volume and red cell volume via stimulation of CaO_2-sensitive aortic bodies).

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