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Oxygen Sensing in the Carotid Body and Its Relation to Heart Failure

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ABSTRACT

This brief review first touches on the origins of the earth's oxygen. It then identifies and locates the principal oxygen sensor in vertebrates, the carotid body (CB). The CB is unique in that in human subjects, it is the only sensor of lower than normal levels in the partial pressure of oxygen (hypoxia, HH). Another oxygen sensor, the aortic bodies, are mostly vestigial in higher vertebrates. At least they play a much smaller role than the CB. In such an important role, the many reflexes in response to CB stimulation by HH are presented. After briefly reviewing what CB stimulation does, the next topic is to describe how the CB chemotransduces HH into neural signals to the brain. Several mechanisms are known, but critical steps in the mechanisms of chemosensation and chemotransduction are still under investigation. Finally, a brief glance at the operation of the CB in chronic heart failure patients is presented. Specifically, the role of nitric oxide, NO, is discussed.
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Oxygen is in one sense the most vital substrate the organism must capture from the environment. The human organism cannot survive on its oxygen stores for >2 min and a few seconds. At 6 min of anoxia, irreversible tissue damage occurs. So a real question could arise: Whence came this vital substrate, oxygen? Current theory has the age of the cosmos at ~8 billion years, with the age of the earth at ~4.6 billion years. But oxygen did not exist on the earth at that time. One conjecture has the origin of life on earth at ~3.8 billion years ago (50). But the planet was still anoxic, so to speak. Early life forms, surviving on anaerobic metabolism, would have been oxidized by the present levels of oxygen (21%). Oxygen in the earth's early atmosphere arose from the large changes in the earth's mantle (38), from UV radiation splitting of water. Subsequently, and most importantly, photosynthesis was the major source of oxygen (19). During water splitting, hydrogen, being lighter, escaped into space. Oxygen, being heavier, went into rocks and into the ocean. Even though photosynthetic bacteria are thought to have arisen ~3.4 billion years ago, earth was still relatively anoxic until ~1.7 billion years ago, oxygen being ~1% of the earth's atmosphere (19, 50). In the eons between 1.7 billion and 540 million years ago, oxygen levels began to increase. The rise in oxygen, due to the increased photosynthesis, enabled a great life event to occur, the Cambrian Explosion of multicellular plants and animals (34, 50). But across the eons of time and evolution, the levels of oxygen have varied enormously, reaching 35% in the late Carboniferous and early Permian periods, before falling to 15% in the late Permian (~250 million years ago). But oxygen peaked again at 25%–30% in the late Cretaceous/ early Tertiary periods (~100 million years ago), and then fell to its present level in the late Tertiary (19). In summary, over evolutionary time the reactivity of oxygen has served to modulate its own accumulation in the atmosphere. Too high levels produced oxygen toxicity suppressing plant growth and photosynthesis. Further, when levels exceeded 25%, even the rain forests would catch fire (19). Oxygen levels would fall. Thus, the biosphere has regulated atmospheric oxygen at a level genial to itself throughout the modern age of plants and animals.

The unique Oxygen Sensor in vertebrates which initiates cardiopulmonary reflex maneuvers in response to a low oxygen

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challenge is the carotid body (CB) located near the carotid sinus, the principal blood pressure regulating sensor. Both are near the bifurcation of the common carotid artery into the internal and external carotid arteries (Fig. 1). Another oxygen sensor, the aortic bodies, are somewhat vestigial in higher vertebrates. At least they play a much smaller role than the CB. For example, individuals whose CBs were resected, show a permanent abolition of hypoxic ventilatory responses (17, 43, 44).

An impressive array of respiratory, cardiovascular, endocrine, and renal reflex responses follow stimulation of the CB (Fig. 2). For example, the frequency and depth of breathing increases. Somewhat paradoxically, airways resistance also increases. Airways secretion increases. The CB stimulates the sympathetic nervous system with a resultant increase in cardiac output as well as an increase in total peripheral resistance. On the other hand, the resistance of the bronchial vascular and pulmonary vascular trees is reduced. The release of cortisol is increased. And in the kidney, CB stimulation increases renal sodium and water excretion in normoxic normotensive animals (10, 11).

The CB is a tiny organ. In normal human subjects, the CB has a mean weight (±SD) of 18 ± 5.6 mg (39). The CB is comprised of transmitter-containing glomus cells (GC; ~10 μm in diameter), type II cells which are supportive and envelope the GCs, an extensive vasculature, afferent nerve fibers having their cell bodies in the petrosal ganglion and their axons extending to the nucleus tractus solitarius in the medullary brainstem, some fat and connective tissue (Figs. 1 and 3). Stimulation of the organ occurs not only in the face of arterial blood having a low partial pressures of oxygen (hypoxia; HH; P_aO_2 < 80–85 mm Hg), but also having a low pH (pH_a <7.34), low plasma glucose (<5 m*M*), and elevated partial pressures of carbon dioxide (P_aCO_2 > 40 mm Hg).

Carbon monoxide can also render a subject hypoxic. But in this case, the P_aO_2 could be perfectly normal while the O_2 content of the arterial blood is low (<15 vol%), due to the binding of the CO by the hemoglobin, preventing the binding of O_2. This is sometimes referred to as carbon monoxide hypoxia (COH). Interestingly, COH does not stimulate the CB. Though the O_2 needs of the CB are considerable, it can derive all the O_2 it needs from the O_2 dissolved in the plasma as it passes through at such a high flow. Blood flow through the CB was estimated in cats, and was reported to be ~2 L/min/100 g tissue (4, 25, 31).

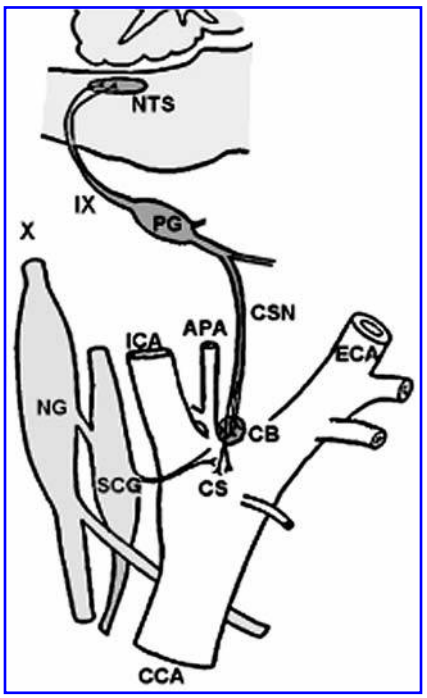

FIG. 1. Carotid body area on the left side of a preparation in the supine position (on its back). Though anatomically tiny, the CB is of major importance to the organism, and is strategically placed at the entrance of the ICA which carries blood to the brain where neurons are exceedingly dependent on oxygen and glucose for their normal operation. When the PO_2 of arterial blood is low, the CB sends signals to the brainstem in an effort to reestablish energy homeostasis. APA, ascending pharyngeal artery; CB, carotid body; CCA, common carotid artery; CS, carotid sinus; CSN, carotid sinus nerve; ECA, external carotid artery; ICA, internal carotid artery; IX, 9th cranial nerve (glossopharyngeal); NG, nodose ganglion; NTS, nucleus tractus solitarius; PG, petrosal ganglion; SCG, superior cervical ganglion; X, 10th cranial nerve (vagus).

A commonly accepted sequence of events during stimulation by HH is: (a) HH acts on an O_2-sensitive structure in the glomus cell (GC); (b) K^+ conductance decreases; (c) this serves to depolarize the GC; (d) the depolarization activates

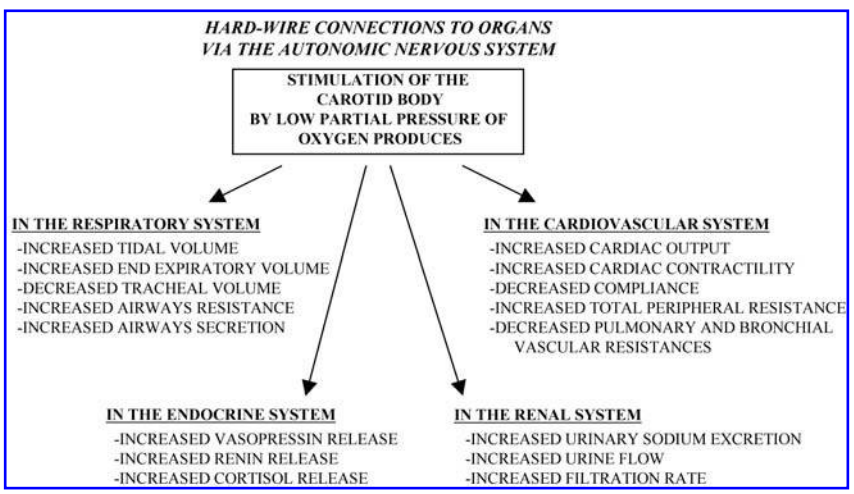

FIG. 2. Hard-wire connections to organs via the autonomic nervous system. The plot gives several of the responses that could occur upon stimulation of the CB. However, an individual response might not be observed because it is being overridden by another response. For example, the impact of the sympathetic nervous system on the cardiovascular system is attenuated by input from the pulmonary stretch receptors in the lungs. Stimulation of the CB increases sympathetic nervous system output, but with a rise in blood pressure, the CS acts as a brake on this output.

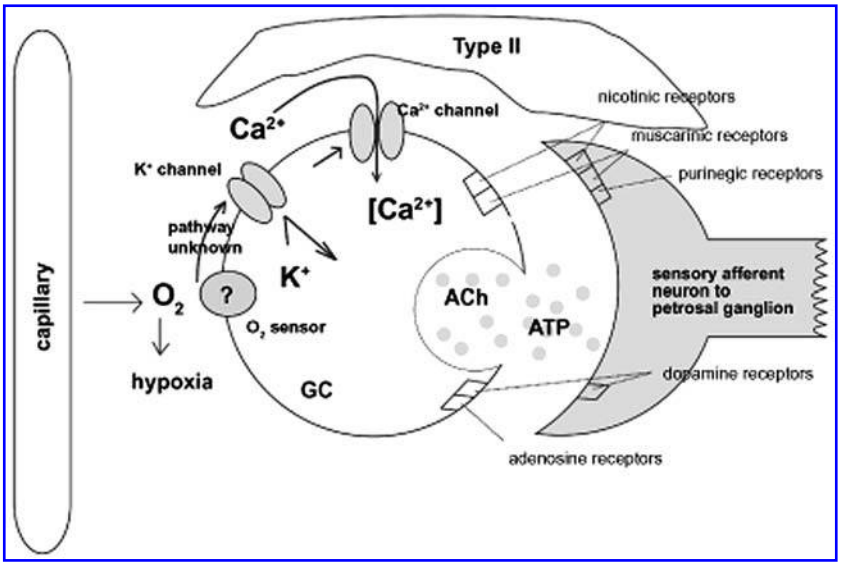

FIG. 3. A simplified macroscopic view of some of the cellular components in the CB. Usually GCs are in clusters called glomeruli. Cf. text for the sequence of events during stimulation by hypoxia. GC, glomus cell; Type II, sustentacular cell; Vm, membrane potential.

voltage-gated calcium channels; (e) extracellular calcium enters the cell; (f) this acts on transmitter-containing vesicles which move to the GC membrane, and the transmitters are exocytosed into a synaptic-like cleft between the GC and the afferent neurons abutting on it; (g) the transmitters bind to these receptor-containing neurons and also back onto GC autoreceptors; (h) an action potential is initiated in the afferent neuron and travels to the petrosal ganglion and then on to the nucleus tractus solitarius in the medulla; (i) the signal is processed in the central nervous system; (j) reflex respiratory and cardiovascular responses ensue; and (k) transmitters acting back on GC autoreceptors influence the further release of the GC's transmitters. Currently, acetylcholine (ACh) and ATP are considered to be essential excitatory transmitters, at least in the rat and cat (10, 24, 36, 45). Dopamine and norepinephrine, also stored in the GCs, tend to modulate or attenuate excitation (18). Direct cell–cell communications between GCs and between a GC and an afferent nerve ending also modulate the excitation of the CB–nerve complex (9).

The precise molecule which "senses" the changes in plasma pO_2 is now under intense investigation (22). Several candidates have been proposed as the oxygen sensor, such as heme oxygenase-2 (26, 48), NADPH oxidase (1, 2, 15), and AMP-activated protein kinase (AMPK) (7, 8).

One current theory suggests that heme oxygenase-2 functions to alter BK channel dynamics under different oxygen tensions (48, 49). BK channel inhibition by hypoxia appears to be mediated by membrane-delimited molecules. Functional proteomics and genetic manipulations point to heme oxygenase-2 as a key mediator between hypoxia and BK channel activity. For example, in the presence of oxygen, heme oxygenase-2 together with NADPH enhances BK channel activity. Hypoxia, however, reduces BK channel activity. But whether the hemoxygenase-2/BK channel pathway is applicable only to the rat CB remains unclear. For example, a recent study reported that in heme oxygenase-2 deficient mice the hypoxia-induced release of catecholamines was not altered (26).

NADPH oxidase is thought to couple changes in oxygen tension to K^+ channel activity via reactive oxygen species (ROS) production in proportion to available oxygen. However, the production of ROS in GCs does not necessarily correlate to oxygen tension (14, 16). Carotid body function remains intact after sequence disruption of the gp91phox gene, a NADPH oxidase component (15). On the other hand, deletion of another component of NADPH oxidase, $p47^{phox}$, enhanced hypoxia-induced responses of GCs (K channel inhibition, increase in intracellular Ca^{2+}, increased afferent nerve discharge) (16). These data suggest that NADPH oxidase does not function as initially hypothesized (1), although it is an important factor in the hypoxic chemotransduction machinery.

AMPK, activated in response to increased cellular ATP consumption or to reduced ATP supply, appears to be localized close to the cell membrane in GCs (8). It may function to link mitochondrial oxidative phosphorylation to K channel inhibition or to Ca channel activation (7,8). Thus far, data are compelling, but further studies are necessary to determine if the levels of oxygen which activate AMPK are in the range of carotid body excitation.

Potassium channels are clearly involved in this critically important step in O_2 sensing. The presence of oxygen-sensitive potassium channels in the CB was first established in 1988 (23). However, the molecular identities of hypoxic-sensitive K^+ channels are extremely diverse. In the rat, Ca^{2+}-activated K^+ channels (also called BK or maxi-K^+ channels) (29) and background TASK-like K^+ channels (47) have been established as oxygen-sensitive K channels. On the other hand, Kv4.1 and Kv4.3 (Kv4.3-1 variant) were identified as oxygen-sensitive channels in the rabbit (32). We have found that BK channels are extremely sensitive to a small decrease in O_2 tension in DBA/2J strain of mice (27). At a pO_2 of 70 mm Hg, 40% of voltage-dependent K^+ current was inhibited. This portion of K^+ current is iberiotoxin-sensitive (a highly specific BK channel antagonist). Further, during severe hypoxia (pO_2 = 10 mm Hg) Kv3 channels are also inhibited in the C57BL/6J mouse (30). But significantly more research must probe more deeply into this unknown.

CB malfunction has been implicated in chronic heart failure (CHF). CHF is a leading cause of death in the United States.

Reportedly, 80% of men and 70% of women under the age of 65 with CHF will die within an 8-year period (42). A second pathophysiological status involving the CB and linked to CHF is obstructive sleep apnea (OSA). The Sleep Heart Study suggests that OSA increases the relative odds of having CHF by 2.2-fold (35). CHF patients have a sustained activation of the sympathetic nervous system and heightened CB chemosensitivity (5, 6, 28, 33, 41). It is thought that oxygen-free radicals are involved within the CBs. Significant experimental models have suggested that the enzyme neuronal nitric oxide synthase (nNOS) is inhibited (33). Hence, there is not the normal level of nitric oxide (NO). NO reduces CB neural output to the brainstem (3, 45) at least in part by reducing the release of the excitatory neurotransmitter ACh (12, 13). The absence, or reduced presence, of NO, therefore, participates in the increased CB neural output. This provokes the increased sympathetic nervous system output, which tends to trigger lethal ventricular arrhythmias (28). NO is thought to increase K^+ conductance, stimulating a repolarization of the CB and a reduction in the output of excitatory neurotransmitters. The NO can act through a second messenger system involving cGMP (20, 21 37). Or it can act directly on Ca^{++} channels modulating the entrance of extracellular calcium (40).

Clearly more investigation is needed before the CB can be targeted as a promising locus for therapeutic intervention in treating chronic heart failure.

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ABBREVIATIONS

AMPK, AMP-activated protein kinase; CB, carotid body; GC, glomus cell in the CB containing the vesicularized transmitters; HH, hypoxia generated by a decreased partial pressure of oxygen; TASK, TWIK-related acid sensitive K channel; it is oxygen-sensitive; TWIK, tandem P domain weak inwardly-rectifying K channel.

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