

## The Carotid Body: Terrestrial Mammals' Most Important Peripheral Neuroreceptor?

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Received date: October 18, 2016; Accepted date: December 28, 2016; Published date: December 30, 2016

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### Abstract

The carotid body (CB) is a tiny structure, bilaterally located at the bifurcation of the common carotid artery into its internal and external branches, is innervated by a branch of cranial nerve IX, and sends its neural output to the nucleus tractus solitarius in the medulla. Arterial flow through the CB is the highest of any organ ever measured. The CB is the unique sensor of decreases in PaO<sub>2</sub>, but is also stimulated by low glucose as well as increases in P<sub>a</sub>CO<sub>2</sub>, [H<sup>+</sup>]<sub>a</sub>, temperature, and osmolarity. Hypoxia-generated increases in neural activity result from K<sup>+</sup> channels in the CB's neurotransmitter-containing glomus (Type I) cells being blocked; this depolarizes the cells allowing calcium to enter, which promotes the movement of the glomus cells' transmitter-containing vesicles to exocytose ACh and ATP into the gap between cell and an abutting afferent fiber, where these agents bind to cholinergic and purinergic postsynaptic receptors. Stimulation of the CB's provokes reflex responses in the respiratory, cardiovascular, endocrine and renal systems. Recent research has identified the CB's malfunctioning in chronic heart failure (CHF). The decreased blood flow in this pathology reduces shear stress on the endothelial cells of the CB's vasculature, reducing the level of critically important molecules, and making the CB hypersensitive. The increased neural output from the CB's promotes an increase in output of the sympathetic nervous system which has a deleterious impact on breathing, cardiovascular and renal function. Techniques have been found in animal models that reduce the CB's impact during CHF. The very large role of this tiny structure in both health and disease underline its organismal importance.

**Keywords:** Carotid body; Carotid artery; Cranial nerve IX; Neurotransmitter; Neural tissues

### Introduction

By far most animal life of which we are aware needs oxygen, the waste product of photosynthesis, for life. They also need glucose from food, and fluid. The human organism can generally survive without food intake for a month; without fluid, for several days, perhaps a week. But how long can this organism survive without oxygen? Well, one answer to that question could be gained by seeing how long one could hold his/her breath. That's usually not longer than two minutes. And depriving the human organisms of oxygen for more than four to five minutes would initiate irreversible damage to most tissues, especially neural tissues. Why? Why is oxygen so immediately necessary? For the heart to beat, for the diaphragm to contract, to think, to walk across the room, all these actions require energy. And oxygen plays a critically essential role involved in the last step of the mitochondria's genesis of adenosine triphosphate, ATP, the biological energy needed for life's activities. Every cell in the body has at least one such organelle. Skeletal muscle cells have many more than one. The number of mitochondria is usually proportional to the activity of the cell. Therefore, a mini review of how oxygen is regulated/controlled in the human organism might be helpful.

### Carotid body structure

In most terrestrial mammalian species a structure called the carotid body (CB) is the primary detector and regulator of oxygen in the

organism. The CB is a bilaterally located structure near the bifurcation of the common carotid artery into its internal and external branches. It is quite tiny, football-like in shape with axes measured in millimetres. In 42 humans mean dimensions were 3.3, 2.2 and 1.7 mm; and in 57 control subjects the mean weight of the CB was 18 mg [1]. However, blood flow through the structure is the largest through any structure ever measured. In the feline model flow has been measured at greater than 2.2 L/min/100 gm tissue. The CB is composed of neurotransmitter-containing glomus (Type 1) cells, usually arranged in clusters called glomeruli. Some of these agents are excitatory such as acetylcholine (ACh) and ATP; others tend to attenuate neural output from the CB such as dopamine, norepinephrine. Several other neurotransmitters are contained in these glomus cells. A second type of cell (sustentacular, Type 2) seems to function in a supportive role; but current thought also has the Type 2 cell participating in the chemical activity of the CB [2]. Abutting on the glomus cells are afferent neurons (branches of cranial nerve IX, the glossopharyngeal) having their cell bodies in the petrosal ganglion. The axons of these ganglion cells insert into the nucleus tractus solitarii (NTS) in the medulla. There are many more glomus cells than afferent neurons. And there is great synaptic complexity within the CB. An afferent neuron undoubtedly branches, perhaps several times, to innervate several glomus cells. And there are gap junctions between the glomus cells [3].

### Carotid body responses to stimuli

The CB might well be considered the most important interoreceptor in the organism because of what it (1) is responsible for under normal resting conditions, up to 40% normal respiration [4], (2) can do when

stimulated in terms of the reflex responses it provokes [5,6] (3) does during sleep apnea [7,8], (4) does in the organism in the pathology of chronic heart failure (CHF) [9]. But first it would be helpful to see how the more common stimuli to the CB increase its neural output via the petrosal ganglion to the NTS. The CB is the organism's unique detector of a decreased partial pressure of oxygen in the arterial blood ( $P_{aO_2}$ ). The aortic bodies spread across the arch of the aorta also respond to a lowered  $P_{aO_2}$ , but the focus of this review is on the CB. Current thinking regarding the mechanisms involved in the increased CB neural output in response to lowered  $P_{aO_2}$  is based on the effect of hypoxia closing some of the K channels in the CBs' glomus cells. Blocking the normal exiting of K ions elevates the resting membrane potential of the glomus cell; e.g., from -65 mV to -49mV to -30mV. When this depolarization reaches a certain level, activation of voltage-gated calcium channels open, and extracellular calcium rushes into the cell adhering to neurotransmitter-containing vesicles. These vesicles approach the inner surface of the glomus cell and dock via a docking protein such as synaptin 1. The vesicles then exocytose their contents into the synaptic-type cleft between the glomus cell and the afferent nerve fiber. ACh, for example, binds to a nicotinic or muscarinic post-synaptic receptors located on the fiber, initiating an action potential which proceeds up to the petrosal ganglion and on to the NTS, whereupon the neural activity is forwarded to respiratory- or cardiovascular-related centers in the medulla and pons of the CNS. Pre-synaptic cholinergic receptors on the glomus cell regulate the output of this neurotransmitter. Arterial blood with a normal  $P_{aO_2}$  but with carbon monoxide (CO), reducing the oxygen content of the blood, does not stimulate the CB. Oxygen's partial pressure is the key factor. The reason for this is that blood flow through the CB is so very fast. So even though the metabolism of the CB is quite significant, the amount of oxygen needed is supplied by the physically dissolved oxygen in the plasma [3,10].

Carbon dioxide ( $P_{aCO_2}$ ) also stimulates the CBs, as does glucopenia [11], increases in temperature and osmolarity [10]. The mechanism for  $CO_2$  stimulation is less well understood. But one hypothesis has the  $CO_2$  molecule diffusing from the blood into the glomus cell where it creates an intracellular acidosis. This activates an amiloride-sensitive  $Na^+/H^+$  exchanger which expels the  $H^+$  while absorbing a  $Na^+$  ion. Simultaneously a  $Na^+/Ca^{++}$  exchanger/transporter begins to remove the  $Na^+$  from the glomus cells in exchange for  $Ca^{++}$ . The  $Ca^{++}$  adheres to vesicles, which then exocytose their contents into the synaptic-type cleft. Other explanations have been presented in detail [12,13].

NO is well known to attenuate the CBs' hypoxia-induced increase in neural output [14]. At least part of this reduction is due to NO's ability to reduce the release of ACh and ATP, excitatory neurotransmitters, from the CBs' glomus cells [15,16]. A second gasotransmitter,  $H_2S$ , also has activity in the CBs. But its role therein is still a matter of some confusion, and may be a matter of species differences [17-19]. Much literature supports  $H_2S$ 's role via the ATP-sensitive K channel to relax vascular smooth muscle and in human airways smooth muscle cells [20]. Although it has also been seen to stimulate CB neural output, it has been seen to reduce the level of ACh and ATP release from *in vitro* challenged cat CBs [21].

Stimulation of the CBs can produce an impressive array of reflex responses [4], (1) The Respiratory System responds with increases in frequency and tidal volume of breaths, an increase in functional residual capacity and airway secretions. (2) The Cardiovascular System responds via the Autonomic Nervous System increasing cardiac contractility, cardiac frequency (after an initial bradycardia), cardiac

output, peripheral vasoconstriction in several vascular beds, but a reduction in the vascular resistance of beds in the eye, adrenal glands, and bronchial circulation. (3) The Endocrine System's adrenal medulla secretes more epinephrine via stimulation by the sympathetic nervous system. The adrenal cortex also is affected by ACTH, a polypeptide tropic hormone produced and secreted by the anterior pituitary gland. It is an important component of the hypothalamic-pituitary-adrenal axis, and is often produced in response to biological stress. Its principal effects are the increased production and release of cortisol by the cortex of the adrenal gland. In the canine model the CBs seem to be the principal chemoreceptor influence on cortisol secretion rate during hypoxia. But there is a non-CB mediated release during hypoxia [22]. (4) The Renal System is also affected by CB activity [23]. CB stimulation increases water and sodium excretion in the kidney regardless of any change in the blood pressure. This effect is seen in animal models, and in human subjects with the use of almitrine, an agent which stimulates the CBs [24]. These effects are abolished with a sectioning of the carotid sinus nerves carrying chemoreceptor information to the NTS.

### Carotid body in heart disease

The activity of CBs is intimately involved in the pathological dimensions of congestive heart failure (CHF) [9]. In this condition the patient's blood flow is reduced throughout the body [25]. This includes the carotid arteries. The reduced blood flow within the carotid bodies reduces the shear stress on the luminal surfaces of the vascular endothelial cells [26]. Normal blood flow producing normal shear stress keeps the transcription factor KLF2 [26,27] at normal levels. This agent is responsible for maintaining NO at normal levels. NO is well known to attenuate the CBs' hypoxia-induced increase in neural output [14]. At least part of this reduction is due to NO's ability to reduce the release of ACh and ATP, excitatory neurotransmitters, from the CBs' glomus cells [15,16]. Hence, in CHF the higher output from the CBs and their increased sensitivity to stimuli generates an increase in output from the sympathetic nervous system (SNS). This has several deleterious effects: puts the patient at higher risk for ventricular arrhythmias, induces autonomic imbalance [28,29] and irregularities in cardiac frequency while locking the respiratory pattern into sympathetic output, and interrupts normal kidney function [28].

Techniques attempting to abolish or correct the malfunctioning CBs in animal models or human subjects have been tried. Among such are (1) CB ablation by freezing the structure [28], or outright removal in human subjects [30]; (2) instilling a program of increased exercise which increases cardiac output, and, therefore, blood flow in the CBs; (3) administration of statins which upgrade KLF2 [27,31]; (4) use of a lower calorie diet. All techniques have enjoyed some degree of success.

### Conclusion

Given the above lore about the CBs it does appear that the structure seems not only to be terrestrial animals' most important interoreceptor, but it could be called a "Paradox of Evolution". The CB, so tiny in size, and having (1) such a large impact on maintaining the homeostasis of the organism, and (2) being involved in such deleterious consequences of a major world-wide pathology, CHF, render it a truly amazing component of the living organism. It is difficult to designate a more important peripheral neuroreceptor than the carotid body.

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