MINI OVERVIEW OF A PRIME INTEROCEPTOR: FROM BASICS TO ROLE IN PATHOLOGIES

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ABSTRACT

Frequently overlooked is arguably the most important sensor of the organism’s internal environment, the carotid body (CB). In human subjects this structure alone warns the organism when the partial pressure of oxygen in the arterial blood is becoming insufficient to meet the organism’s needs. But the structure is also stimulated by hypercarbia, glucopenia, acidosis, increases in temperature and osmolality of the arterial blood. Reflex responses generated by a stimulated CB are found in the respiratory, cardiovascular, renal, and endocrine systems. Recent widespread pathologies also involve the CB. A simple, brief overview of this important structure could prove helpful for biomedical investigators focused on other important biomedical issues.

Key words: Carotid body (CB), hypoxia, shear stress, KLF2, hypertension, chronic heart failure (CHF), obstructive sleep apnea (OSA)

INTRODUCTION...WHY PRESENT THIS?

Most busy clinicians and most neuroscientists do not have time to consider this, arguably the most important neuroreceptor regulating the internal environment of the organism. Clinicians must focus on therapy for varieties of neuropathology and many neuroscientists these days are focused on levels of central nervous system (CNS) organization at the subcellular and genetic levels. However, certain other pathologies which create very large public health problems, for example, chronic heart failure (CHF) and hypertension, do involve this tiny neuroreceptor. Consequently, more attention is becoming focused on the carotid body (CB). This would seem to justify a brief overview of the structure…What is it? Where is it? What does it do? How does it work?

WHAT IS IT? WHERE IS IT?

Neurologically, it is a receptor which “tastes” the arterial blood for qualitative changes in composition. Moreover, it is neurologically connected to the CNS in the nucleus tractus solitarii (NTS) through a branch of Cranial Nerve IX through the petrosal ganglion. This tiny receptor is bilaterally located near the bifurcation of the common carotid artery into the internal and external carotid arteries (ICA, ECA). The CB lies in the bifurcation or slightly rostral to it.[1] The carotid sinus, principal detector, and regulator of blood pressure lies caudal to the CB; the sinus structure is found at the base of the ICA. The small branch of Cranial Nerve IX called the carotid sinus nerve carries afferent fiber traffic from both the carotid sinus and the CB. Whereas traffic from the CB stimulates output from the sympathetic nervous system (SNS), traffic from the carotid sinus tends to block SNS output.

WHAT DOES IT DO?

As shown in humans animal model studies, once the CBs are stimulated, the organism responds with an increase in respiratory tidal volume and frequency; further, the functional residual capacity increases. The CBs’ stimulation of the SNA also increases cardiac frequency and contractility.

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However, what impact CB stimulation per se has on the cardiovascular system can only be presented with caution because CB stimulation also affects the respiratory system which has its own impact on the cardiovascular system. Moreover, this effect would be simultaneous with the cardiovascular responses. To avoid this one could paralyze the animal. However, this would have its own effect. Most SNS-stimulated vascular beds vasoconstriction; exceptions are the pulmonary, bronchial, adrenal, and ocular beds which vasodilate. CBs also stimulate an increase in the release of ADH, ACTH, cortisol, and the adrenal medullary epinephrine. Finally, stimulated CBs promote an increase in the release of fractional urinary and sodium excretion.

**HOW DOES IT WORK?**

Human CBs are normally stimulated by hypoxemia (P \(_{O_2}\) <80–85 mmHg), hypercapnia (P \(_{CO_2}\) >45–49 mmHg), metabolic acidosis (pH <7.35), decreased (glucose) (<5 mM), increased temperature, or increased osmolarity, and through other agents (physical and chemical) can stimulate the CBs. However, the CB is the organism’s unique detector of hypoxemia. The CBs’ blood supply comes from a small branch of the ECA. Flow through the CB in the feline model has been measured at >2 L/min/100 g tissue, the highest of any organ measured. Shaped something like an American football the CB’s three dimensions measures only a few millimeters in the three directions, and it weighs ~18 mg.

The CB, which can be bi-lobed, is composed of two types of cells, the Type I (or Glomus) cell which contains neurotransmitters, and the Type II cells which are thought to support and protect Type I cells, though they may also participate in neurotransmission.

Afferent nerve fibers in a branch of the glosopharyngeal nerve (Cranial Nerve IX) about on the Type I cells; the branch also contains a few efferent fibers. Hypoxia acts on some of the K channels in the Type I cells blocking ionic movement; this depolarizes the cell. When its membrane potential reaches high enough, voltage-gated calcium channels open. Extracellular calcium enters and adheres to neurotransmitter-containing vesicles. These vesicles move and adhere to the inner surface of Type I cell using a protein, such as Synaptin 1, synaptobrevin, and other such vesicle-associated membrane proteins. The vesicles exocytose their contents into the synaptic-like cleft between the cell and an abutting afferent neuron(s), binding to nicotinic, muscarinic, dopaminergic, or purinergic receptors. This initiates an increase in neural traffic up the fiber, the carotid sinus nerve, through the petrosal ganglion and on to the medullary NTS. This neural traffic is then fed off to the parasympathetic vagal nuclei and/or the sympathetic nuclei (e.g. paramedian reticular nucleus). In most cases, stimulation of the CBs means stimulation of the SNS.

**ROLE IN VARIOUS PATHOLOGIES**

**Obstructive sleep apnea**

Among the risk factors for this pathology in our characteristically overweight society is obesity. Fat deposits near the upper airways block the passage of air into the lungs. Apnea results simultaneously with the continuing metabolism, lowering P \(_{O_2}\) and elevating P \(_{CO_2}\). This asphyxia combination of gases is a powerful stimulus to the CBs to initiate a breath. The subject subconsciously awakens for a momentary breath. However, during the few second apneic periods, the stimulated CBs to prompt an output not just to breathe but to the SNS to increase neural output. The cardiovascular system responds by generating an increase in arterial blood pressure (ABP). Since apneic episodes during sleep can occur with a frequency of 10–12/h, the attendant increases in ABP, though returning toward normal levels during the non-apneic intervals, coalesce to elevate the subject’s ABP to a degree of nocturnal hypertension. This condition sometimes perdures into daytime hypertension.

**Systemic hypertension**

Significant amounts of work have been done showing in one case that hypertension increases the sensitivity of the CBs to hypoxia and hypercapnia in young men with mild hypertension. The control group of young men could rebreathe from an enclosed container for longer periods and endure a more advanced hypoxia than the mild hypertensive group. A second measure, P \(_{O_2}\), in which the inspiratory effort was blocked after 200 ms found that the hypertensives’ drive was about twice that of the control group. In sum, it does seem that hypertension sensitizes to some degree the CBs’ response even to room air.

**Chronic obstructive pulmonary disease (COPD)**

In emphysema lung tissue breaks down reducing alveolar surface for gas exchange. Further, expiration airways collapse because of the lungs’ increased compliance and failing structure. Air in the lungs becomes trapped. With the next inspiration, the new gas mixes with what had remained, resulting in lower P \(_{A\_O_2}\) values. Alveolar hypoxia generates the hypoxic pulmonary vasoconstrictive (HPV) response. However, the depressed P \(_{A\_O_2}\) also stimulates the CBs. This effect has been shown to attenuate the pulmonary artery vasoconstriction in animal models. If the HPV is too intense, right heart failure is possible allowing fluid accumulation in the lungs and lower extremities. The effect of an elevated P \(_{ACO_2}\) frequently found in COPD patients is offset by the kidney’s retention of bicarbonate, obviating too great a systemic acidosis.

**CHF**

Many patients suffering from CHF have sensitized CBs. One study showed that of the two groups compared, longevity among those with non-sensitized CBs had a 3-year survival rate...
of 76%, while among those with the sensitized CBs, the rate was only 41%. As seen above, the stimulation of the CBs provokes increased neural activity from the SNS. This disturbs respiratory, cardiac, and renal functioning. Consistent with the longevity studies CB removal was suggested as therapy, though this procedure has its own less desirable results. However, in one study a man had one CB removed; and in a second study, six men had both CBs removed. In both studies, significant cardiopulmonary improvement was reported. In the interest of finding therapies alternative to CB removal, studies were initiated to explore what mechanisms in the CBs might be responsible for sensitizing it. Elegant animal studies in the rabbit and rat rendered CHF by the operation of an implanted pacemaker and ligation of a coronary artery, respectively, showed that the decreased systemic blood flow of CHF included reduced CB blood flow. Reduced CB blood flow reduced the shear stress on a mechanical receptor protein on the luminal surface of an endothelial cell in the CB vasculature. This through an intermediate cascade of proteins reduced the level of Kruppel-like Factor 2 (KLF2) in the CB. This, in turn, reduced the level of eNOS, responsible for the genesis of NO, well known to reduce CB output in response to hypoxia. Two therapies resulted from these studies. A mild exercise program improved the status of the CHF animals. Moreover, the inclusion of statins in the diet of the animals likewise improved their status. Statins are known to increase KLF2 levels. The CBs’ multiple roles and activities are very much underappreciated.

However, they do serve as prime guardians of the internal environment, including pulmonary and cardiac function, so very dependent on the autonomic nervous system.

REFERENCES


**How to cite this article:** Fitzgerald RS. Mini Overview of a Prime Interoceptor: From Basics to Role in Pathologies. Asclepius Med Res Rev 2018;1(1):1-4.