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Success/Failure of the Carotid Body's Control of the Organism's Internal Environment

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Introduction

Medical practice has moved from the anecdotally based, and currently uses the evidence-based diagnosis/therapy paradigm for understanding and treating a patient's ill-health. There is a movement to dig more deeply into the genome/environment based area in which the patient's individuality is revealed down to the genes, family history, and subsequent environmental impacts on those structures as a method to gain a deeper understanding of the patient's ill-health. It has been referred to as "Precision Medicine." The goal is a more personalized understanding of the patient's health status and its causes. This plus the almost daily arrival of new drugs for therapy can prevent the physician from keeping in mind the physiological perspective, the components of the patient's internal environment and how these components control the patient's internal environment.

The control of the internal environment of a patient depends largely on the proper functioning of several neural receptors such as the high pressure receptors in the carotid sinus and aortic arch for detecting and regulating, via the autonomic nervous system, the organism's blood pressure. There are low pressure receptors located in the chambers of the heart and terminations of the great veins. There is the carotid and aortic bodies for detecting the composition of the blood, though in human subjects the latter structures are only minimally, if at all, operating. Neural receptors in the airways influence both the respiratory system and the cardiovascular system. Transient receptor potential channels are a recent addition to this list. The 1938 Nobel Prize in Physiology or Medicine was awarded to the Belgian physiologist Corneille Heymans for his discovery of the role of the carotid and aortic mechanisms in the control of ventilation in the dog model.

To survive the organism needs food, fluid, oxygen. Humans can do without food for a month; without fluid, for several days, perhaps a week. But they cannot do without oxygen for more than 4-5 min without doing irreversible damage to all tissues, but especially neural tissue. The carotid body is the unique sensor of decreasing PaO2. Hence, it might be helpful for the busy physician to review this structure and how it reacts to stimulation in health and in a common form of ill-health, chronic heart failure.

Carotid Body Structures and Action

The carotid bodies (CBs) are tiny ovoid structures located bilaterally at the bifurcation of the common carotid arteries into their internal and external branches (Figure 1), approximately behind the angle of the mandible in human subjects. The axial dimensions of this tiny structure are 3.3 × 2.2 × 1.7 mm; it weighs in the 14-18 mg range [1], though there tends to be sizeable variations. Unique to this structure is its blood flow which is the highest in any organ that has ever been measured. In the feline model the flow is >2.1 L/min/100 gm tissue [2]. The arterial supply is from the external carotid artery, and the venous outflow is into the internal jugular vein. The CB itself is composed of two types of cells, the glomus (or Type I) cell, which contains a variety of neurotransmitters (NTs) such as the fast-acting excitatory two, acetylcholine (ACh) and adenosine triphosphate (ATP). Dopamine (DA), serotonin (5HT), gamma amino butyric acid (GABA), histamine are also present. In the feline model there are estimated to be roughly 40,000 to 50,000 glomus cells/CB. It is unlikely that each cell contains all the NTs. The second type of cell (Type II) is sustentacular, though some recent studies conclude that it may well participate in the handling of the NTs [3].

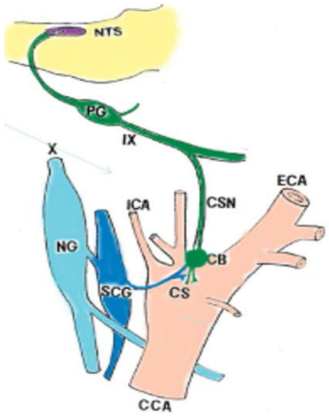

Figure 1: Anatomy of Carotid Body Area. Anatomical sketch of the carotid sinus/CB area showing principal structures. NTS: Nucleus Tractus Solitarii; PG: Petrosal Ganglion; IX: Ninth cranial nerve (glossopharyngeal); X: Tenth cranial nerve (vagus); CSN: Carotid Sinus Nerve; CB: Carotid Body; CS: Carotid Sinus; ECA: External Carotid Artery; ICA: Internal Carotid Artery; CCA: Common Carotid Artery; SCG: Superior Cervical Ganglion; NG: Nodose Ganglion. CB's arterial supply is off a branch of the ECA, the ascending pharyngeal artery. CB's venous outflow, not shown, flows into the internal jugular vein.

As stated above the CBs are stimulated by hypoxemia. A PaO_2 of less than the normal value of 95-100 mmHg will stimulate a neural output from the CB. Decreases in arterial glucose concentration [4] and increases in H^+ concentration or in $PaCO_2$ ($PaCO_2$ >38-42 mmHg) will also produce an increase in CB neural output [5].

Besides these chemical agents, increases in plasma heat and osmolarity [2], such as is found in exercise, will also increase CB neural output. A branch of the IX cranial nerve (glossopharyngeal), called the carotid sinus nerve, is composed of afferent fibers abutting on the glomus cells. In classical neurology these would be called dendrites since they deliver CB neural output to their cell bodies located in the petrosal ganglion (near the tympanic bulla). Axons from the ganglion proceed to the nucleus tractus solitarii (NTS) in the medulla. Evidence suggests hypoxemia stimulates the CB in the following steps. Low oxygen depresses the flow of K^+ ions out of the glomus cells. This depolarizing action elevates the resting membrane potential and so activates voltage-gated calcium channels. Extracellular calcium enters the glomus cells and attaches to the NT-containing vesicles which then proceed to the inner surfaces of the glomus cells where they dock by way of the protein syntaxin or synaptobrevin. They then exocytose their contents into the synaptic type cleft between the glomus cell and the abutting afferent neuron. ACh will attach to both nicotinic and muscarinic receptors on these afferent neurons, while ATP attaches to purinergic receptors on the afferent neurons. Similar, but not identical, processes are involved with CO_2 and glucose stimulation [4,5].

Two interesting points about this system. Carbon monoxide (CO) which certainly lowers the oxygen content of the arterial blood does not stimulate the CB. CB metabolism is, however, very high [2]. This suggests that the CB apparently can derive enough oxygen from the physically dissolved fraction because of the extremely high blood flow. It does not depend upon the oxygen chemically bound to hemoglobin. It is the partial pressure of oxygen (PaO_2) which is important for CB stimulation. Secondly, the carotid sinus, a vascular outpocketing at the base of the internal carotid artery, is only a few millimeters proximal to the CB. The sinus detects changes in blood pressure, and sends many fibers from its mechanically sensitive bulge up the same carotid sinus nerve as does the CB. So two types of afferent fibers travel in this nerve. It is interesting to recall that stimulation of the carotid sinus mechanoreceptor fibers puts a brake on the neural output from the sympathetic nervous system (SNS), whereas neural traffic in fibers from the CB provokes an increase in neural output from the SNS.

Stimulation of the CBs produces an impressive array of systemic reflex responses: respiratory, cardiovascular [6,7], renal [8,9], and endocrine [10]. Figure 2 presents a view of these reflex responses. Studies have shown that as much as 40% of quiet breathing is due to CB neural output [11]. Since the CB is a rate-sensitive structure, perhaps the oscillation of blood-gas values, with the inspiration/expiration cycle, is responsible for this phenomenon. And as stated above any steady decrease in PaO_2 or increase in $PaCO_2$ stimulates. In obstructive sleep apnea when both occur simultaneously, the momentary large stimulus to the CBs accounts for the arousal from sleep to take a breath [12].

Carotid Body and Chronic Heart Failure

Clinical evidence exists (Figure 3) that chronic heart failure (CHF) has an impact on the CBs [13]. Part of this impact is to increase output from the sympathetic nervous system (SNS) due to hypersensitive CBs. Breathing is affected as is cardiac performance. Seminal animal studies with rabbits and rats on the mechanisms involved have been provided by the group at the University of Nebraska Medical Center [14,15]. CHF in the rabbits was generated by inserting a pacemaker and a regimen of very rapid pacing for weeks after which CHF was present. The rats underwent coronary artery ligation to generate CHF. This produced serious deleterious effects on breathing (Cheyne-Stokes pattern), in the heart (reduced LV ejection fraction), renal vasoconstriction, and reduced urine output. Survival statistics showed the CHF animals lived much shorter lives than the control animals. This reflected the data from the human subjects (Figure 3) in which one group of subjects had a relatively normal CB sensitivity (77% 3-year survival rate) while a second group had sensitized CBs (41% 3-year survival rate).

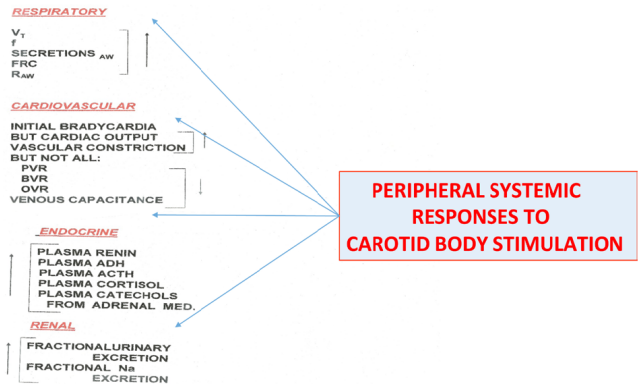

Figure 2: Reflex Responses to Carotid Body Stimulation. Diagram of the several systemic reflex responses to CB stimulation. VT: tidal volume; f: respiratory frequency; AW: airways; FRC: functional residual capacity; RAW: airways resistance; PVR: pulmonary vascular resistance; BVR: bronchial vascular resistance; OVR: ocular vascular resistance; ADH: antidiuretic hormone; ACTH (Adrenocorticotropic hormone). Up arrows, increase; Down arrow, decrease.

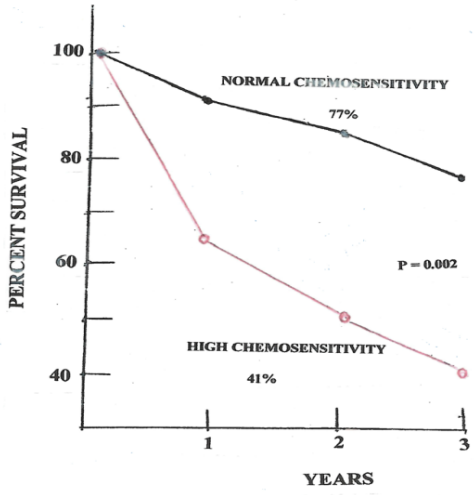

Figure 3: Clinical Data: CHF Survival Depending on CB Sensitivity. Sketch of survival between two groups of patients with CHF. One group did not have the sensitized CBs normally found in CHF. This group (n=53) had a three-year survival rate of 77%. A second group (n=27) did suffer with highly sensitized CBs. The three-year survival rate for this group was only 41%. Significant differences at the years after diagnosis (Adapted from Ponikowski [13]).

Given the clinical data and the animal studies it became important to see how the influence of the CBs could be muted or attenuated. Most radical, of course, would be the removal of the CBs. Niewinski and his colleagues [16] did exactly that in a 56 year old male who had presented with a serious heart failure condition (NYHAII). Six months after a unilateral removal of a CB the patient's heart rate variability had subsided, apneas and dyspneas were also reduced and there was an increase in exercise capacity. A second study also proved effective [17]. In the animal studies freezing major sections of the CBs proved to be an effective in situ denervation [18]. Breathing improved with a reduction of apneic/hypopneic events per hour. LV end systolic and diastolic volumes were reduced. Renal sympathetic nerve traffic, also an index of CB neural output, was reduced restoring kidney blood flow and urine output [14].

Another method for reducing CB neural output was a program of exercise [19]. During exercise, of course, cardiac output increases. This elevates blood flow throughout the organism including the common carotid artery and, therefore, the CBs. This technique had the same beneficial effects as did denervation of the CBs by freezing. This result suggested that blood flow was a major factor in sensitizing the CB. The group tested this by inserting carotid artery occluders. A program of regularly occluding the arteries, reducing blood flow to what was observed in CHF, produced the same effect as CHF [20]. Hence, the next question was what factor in blood flow produced the sensitization of the CB.

Molecular Mechanisms for Restoring Carotid Body to Normal Activity

Figure 4 diagrams the mechanisms found by the Nebraska Group to be operating in the CB during low blood flow. The mechanism involved a mechanoreceptor protein on the luminal surface of a CB vascular endothelial cell. During normal blood flow the shear stress on this structure stimulated a cascade of intermediate proteins to maintain the appropriate level of Kruppel-like Factor 2 (KLF2). KLF2, in turn, maintained normal levels of nitric oxide synthase (NOS) and the genesis of NO [21]. In a feline in vitro model [22] NO had been found to reduce the hypoxia-induced increase in CB neural output, in part due to the reduction of the hypoxia-induced release of the excitatory NTs, ACh and ATP, from the CBs' glomus cells [23,24].

This Group's further experiments showed that KLF2 was absent in CHF animals. But when KLF2 was inserted into the CBs with an adenovirus injection, CB responses returned towards normal. Finally, in experiments focusing on KLF2 the Group discovered that simvastatin in the diets of the rats was beneficial for maintaining an appropriate level of KLF2 [25,26].

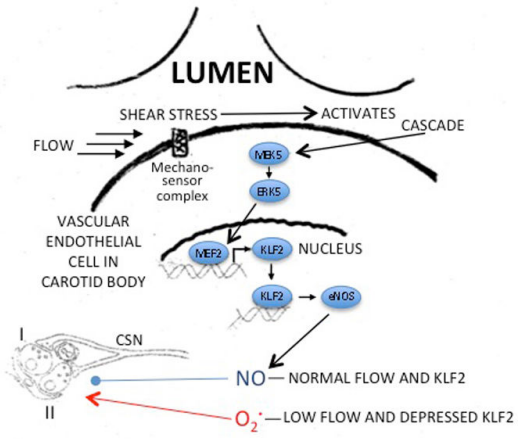

Figure 4: Role of KLF2 in Carotid Body. Sketch of how normal blood flow generating shear stress on CB's vascular endothelial cells impacts on KLF2 via a cascade of intermediate proteins, and ultimately generates NO. Lower flow in CHF reduces shear stress decreasing levels of KLF2 as well as NO. The modulating effect of NO on CB neural output is lost, rendering the CB hypersensitive and increasing CB neural output. This increases SNS neural output with the deleterious effect on breathing, cardiovascular, and renal performance. (Adapted from Garcia-Sancho [21]).

Summary and Conclusion

In spite of its tiny dimensions the CB controls the organism's internal environment under normal conditions by its processing of the arterial material presented to it. When these materials present a threat to the organism as, for example, at altitude, an array of systemic reflex responses attempts to restore the internal environment to the normal status. However, the CB is unable on its own to maintain a normal internal environment in the face of a very common disease, CHF, when pathologies within the respiratory, cardiovascular, and renal systems occur. Clearly personalized or precision medicine constitutes a major step forward in the therapy of patients. But on the more macroscopic level of the patient the role of the internal environment and its neuroreceptor control should not be ignored.

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