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Review Articles

The Human Carotid Body and its Role in Ventilatory Acclimatization to Hypoxia

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The carotid body (CB) is a paired neural crest-derived small ovoid mass of tissue that registers the changes in the arterial blood levels of oxygen, carbon dioxide as well as hydrogen ion concentration and reacts to these changes by the initiation of an appropriate respiratory and cardiovascular response. The human CB shows remarkable structural plasticity and this plasticity underlies the so-called ventilatory acclimatization to hypoxia. The CB morphological changes to high-altitude adaptation include glomus cell hypertrophy and hyperplasia, marked vasodilation and vascular remodeling. The hypoxic CB also shows extraordinary plasticity in different neurotransmitter systems. The altered neurochemical profile of the chemosensory cells comprises elevated catecholamine contents, changes in purinergic mechanisms, up-regulation of nitric oxide metabolism, a marked reduction in peptide levels and production of neurotrophic factors. The structural changes and complex interactions among transmitters markedly influence hypoxia-induced responses in the human CB, thus implying its essential role in ventilatory acclimatization.

Key words: carotid body, high altitude, oxygen homeostasis, structural and neurochemical plasticity, ventilatory acclimatization to hypoxia

Introduction

The carotid body (CB) is the main peripheral arterial chemoreceptor in humans that registers the levels of gases in the blood, eliciting reflex responses to their changes. It is a conglomerate of two juxtaposed cell types: neuron-like glomus cells, which are considered chemosensory cells, and glial-like sustentacular cells, which play a role

in the metabolic support, and have recently been assumed stem cells that behave as glomus cell precursors [6, 8]. The CB is strategically located at the bifurcation of the common carotid artery to monitor blood chemicals just before they reach the brain and thereby to initiate respiratory, cardiovascular, and humoral responses to maintain blood gas homeostasis [for a recent review, see 12]. The phenomenon that helps the body to maintain oxygen homeostasis is called ventilatory acclimatization to hypoxia (VAH), an adaptive process to high altitudes. Certainly, low oxygen levels in blood known as hypoxemia are detected by peripheral arterial chemoreceptors, which accordingly accelerate the frequency and depth of breathing.

There is a large body of current evidence suggesting that the CB plays an important role in the physiological adaptation to high altitude [2, 3, 7, 14, 24]. Specifically, VAH that occurs in humans and several animal models exposed to chronic deficiency in tissue oxygenation called hypoxia [17] is characterized by enhanced CB chemosensory responses [22]. Moreover, the chemosensory transduction and transmission of the hypoxic stimulus, underlying the adaptive process to high altitudes, evoke considerable plasticity of the CB structure and function, as well as modify the neurochemical profile of its cell subpopulations [14].

Structural plasticity of the human CB at high altitude

The vast majority of humans dwell at or slightly above sea level, where the oxygen availability is sufficient. However, at 4000 m the oxygen concentration is only 60% of that at sea level and it gradually decreases with altitude ascent. In addition, when ascending to high altitude atmospheric pressure drops, resulting in a decreased partial pressure of inspired oxygen and saturation of arterial haemoglobin [21]. Globally, it has been estimated that more than 140 million people, i.e. approximately 1.1% of the world's human population, live permanently at altitudes above 2500 meters, defined as high altitude, thus putting these populations at risk of developing chronic mountain sickness. In fact, only three human populations have lived at high altitude for millennia: Andeans on the Andean Altiplano, Tibetans on the Tibetan Plateau, and Ethiopians on the Semian Plateau without apparent life-threatening complications. Obviously, these populations have evolved adaptive physiological phenotypes that aim to increase oxygen delivery into the body.

It has been shown that morphological and functional alterations in the CB occur in people during their acclimatization to sustained hypoxia [3] or pathologically in sea-level patients with emphysema [2]. Initially Arias-Stella and Valcarcel [1] report an increase in the CB size and weight in high-altitude dwellers in the Peruvian Andes at 4330 m and later Heath et al. [11] describe a similar CB enlargement in sea-level patients with emphysema. Heath and Smith [10] have subsequently demonstrated that the CBs of Quechua Indians born and living in the Peruvian Andes are larger than those of mestizos living on the coast [10]. Thus, the physiological acclimatization to high altitude in native highlanders includes a CB augmentation mainly due to glomus cell hypertrophy and hyperplasia, marked vasodilation and vascular remodeling. The increase in vascularity of the hypoxic CB may be a mechanism to increase blood flow and thus of oxygen transport to a hypoxic organ with elevated metabolic activity.

On the other hand, such structural CB adaptation responses to prolonged hypoxia occur in humans not only during long-term acclimatization to high altitudes (**Fig. 1**) but

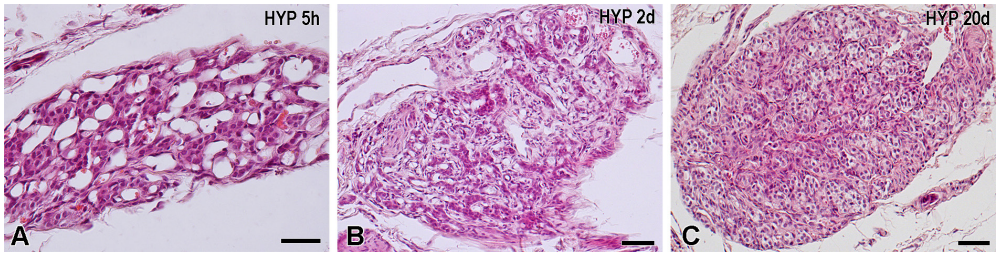

Fig. 1. Hematoxylin and eosin-stained tissue sections showing structural plasticity in the carotid body at **(A)** 5 hours of hypoxia (HYP 5h), **(B)** 2 days of hypoxia (HYP 2d), and **(C)** 20 days of hypoxia (HYP 20d). Note the marked vasodilation of blood vessels and hypertrophy of glomus cells. Scale bars = 50 μm.

also in patients suffering from systemic hypertension and/or cardiopulmonary diseases with concomitant hypoxemia [9]. Indeed, our experiments have revealed that the hypertensive CB in rats could slightly enlarge its parenchyma with no apparent vascular expansion and/or dilation, and increase in extracellular matrix (**Fig. 2**) [4]. Similar CB hyperplasia has also been described in patients with essential hypertension [18]. However, the results of Kato et al. [13] suggest that the CB morphology under hypertensive conditions is rather altered by the effect of sympathetic nerves, and in this way, these structural changes could be secondary to hypertension.

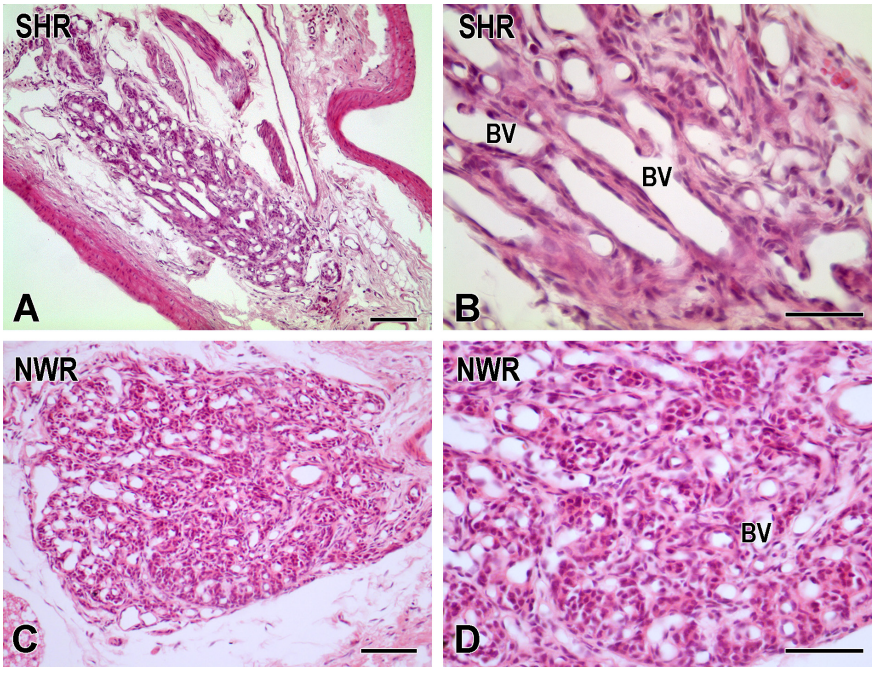

Fig. 2. Structural plasticity of the carotid body under hypertensive conditions in **(A, B)** spontaneously hypertensive rats (SHR) and their comparison with **(C, D)** age-matched normotensive Wistar rats (NWR) in hematoxylin and eosin-stained sections. Note the insignificant enlargement of its parenchyma with an apparent dilation of blood vessels (BV) in SHRs. Scale bars = 50 μm.

It has lately been revealed that the CB structural plasticity depends on the existence of a population of multipotent adult neural crest-derived stem cells, which are quiescent in normoxia and activated during hypoxia to proliferate and differentiate into new glomus cells, as well as smooth muscle and endothelial cells [19].

Neurochemical plasticity of the human CB at high altitude

There is a growing consensus that in addition to the significant cellular rearrangement that culminates in structural plasticity, chronic hypoxia induces neurochemical changes in the chemosensory cells of the CB. It is well established that hypoxia causes glomus cells to depolarize and release both excitatory and inhibitory transmitters, which bind to autoreceptors or postsynaptic receptors on apposed chemoafferent nerve terminals [8]. Furthermore, upon exposure to hypoxia neurotransmitters and neuromodulators released by glomus cells act as paracrine signals that induce proliferation and differentiation of multipotent stem cells and progenitors, thus causing CB hypertrophy and an increased sensory output to the respiratory center in order to correct the condition [20].

Given the central role of ATP and adenosine in CB chemoexcitation, it is not surprising that alterations in purinergic neurotransmitter mechanisms, and particularly in adenosine signaling, have been implicated in VAH [16]. Chronic hypoxia also induces profound changes in other neurochemical systems within the CB such as catecholaminergic, peptidergic and nitrergic systems [23]. Our recent data have indicated that the nitrergic and neurotrophic profile of the CB cell population is also altered in hypertension and this may activate its chemosensitivity [5].

Taken together, current data suggest that complex interactions among transmitters markedly influence hypoxia-induced transmitter release from the CB. It is likely that the up- or down-regulation of these systems may contribute to increased ventilatory and chemoreceptor responsiveness to hypoxia at high altitude.

Conclusion

In conclusion, sustained high-altitude hypoxia induces apparent morphofunctional and neurochemical changes within the human CB, thus implying the plasticity in the cellular and molecular mechanisms of CB chemoreception. It is largely determined as functional changes resulting in increased glomus cell excitability and by neurochemical interactions between a variety of neurotransmitter systems and their receptors in the glomus cells. The CB tends to maintain oxygen homeostasis by marked morphological and neurochemical alterations in animal models of human hypertension as well, so most of the latter may be explained by the altered transmitter phenotype of CB chemoreceptor cells. Knowledge of the mechanisms of CB dysregulation is essential to understand the role of this tiny structure in the human body in various physiological and pathophysiological conditions, including VAH and sympathetically-mediated diseases [15].

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