Institute of Experimental Morphology, Pathology and Anthropology with Museum
Bulgarian Anatomical Society

Acta morphologica et anthropologica, 19
Sofia • 2012

The Human Carotid Body in Health and Disease

N. Lazarov[1,2], *D. Atanasova*[2]

[1]*Department of Anatomy and Histology, Medical University of Sofia, Sofia, Bulgaria*
[2]*Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia, Bulgaria*

The carotid body (CB) is a small paired organ located at the bifurcation of the common carotid artery. It is the only chemoreceptor sensitive to systemic hypoxia in humans. The CB parenchyma is organized in cell clusters (glomeruli), separated by septa of connective tissue and composed of two juxtaposed cell types: type I or glomus cells and type II or sustentacular cells. As a neurovascular structure, the CB is highly vascularized and densely innervated by sensory and autonomic nerve fibers. The neuron-like glomus cells contain numerous dense-cored vesicles storing and releasing neurotransmitters. These include both classical and peptide transmitters. There is evidence that chronic hypoxia induces gene expression, leading to marked morphological and neurochemical alterations in the human CB, thus implying its structural and neurochemical plasticity. These changes could be either physiological during the course of high altitude adaptation or pathological in patients with systemic hypertension or cardiopulmonary diseases with concomitant hypoxemia. Altered structural, neurotransmitter and functional profiles of the human CB are also implicated in various physiological and pathophysiological conditions, including sleep-disordered breathing, congestive heart failure and hypertension. The CB is a neurogenic center in adult life and its stem cells could be potentially useful for cell therapy against neurodegenerative diseases.

Key words: carotid body, chemoreception, chronic hypoxia, neurogenesis, structural and neurochemical plasticity, human

Introduction

The carotid body (CB), also known as the glomus caroticum, is a small, neural crest-derived paired ovoid mass of tissue, around 2 mm large in humans. It is situated in the loose connective tissue of the carotid bifurcation, between the external and internal carotid arteries [2]. This location is strategic for monitoring blood chemicals just before they reach the brain, an organ that is critically sensitive to oxygen and glucose deprivation.

The CB is the main peripheral chemoreceptor while the aortic bodies only play a limited role in chemoreception in humans. The carotid chemoreceptors register the arterial blood tension of O_2, CO_2 and pH, and respond to their level changes by regulating breathing. The organ also plays an essential role in initiating an appropriate cardiovascular response to hypoxia, hypercapnia and acidosis. It has recently been shown that the CB is a glucose sensor too, activated by hypoglycemia [reviewed in 11].

Embryologically, the CB develops from the mesenchyme of the third branchial arch next to the third arch artery [17], at the same time when neural crest cells, blood vessels, and nerve fibers from sympathetic and cranial nerve ganglia invade the mesenchymal primordia in its wall [8]. In addition, neural crest cells differentiate into the two cell types of the CB.

Structural organization of the human carotid body

The cellular parenchyma consists of two types of cells commonly arranged in clusters called glomeruli which represent the basic morphofunctional unit of the CB [5, 13]. The lobules of glomic tissue are separated from each other by septa of connective tissue, which converges upon the surface to form a capsule for the whole organ (Fig. 1A). Mast cells are commonly seen in the human CB and they are largely confined to the interlobular connective tissue, closely apposed to and around small blood vessels [7].

The most striking structural features of the CB are its rich vascularization and dense innervation. The CB contains the most abundantly vascularized tissue in the human body; hence it has the highest blood flow per tissue weight of any organ. It is supplied by one or more glomic arteries, arising from the external carotid artery [19]. A profuse capillary network travels in the fibrous stroma and gives a pink-colored ap-

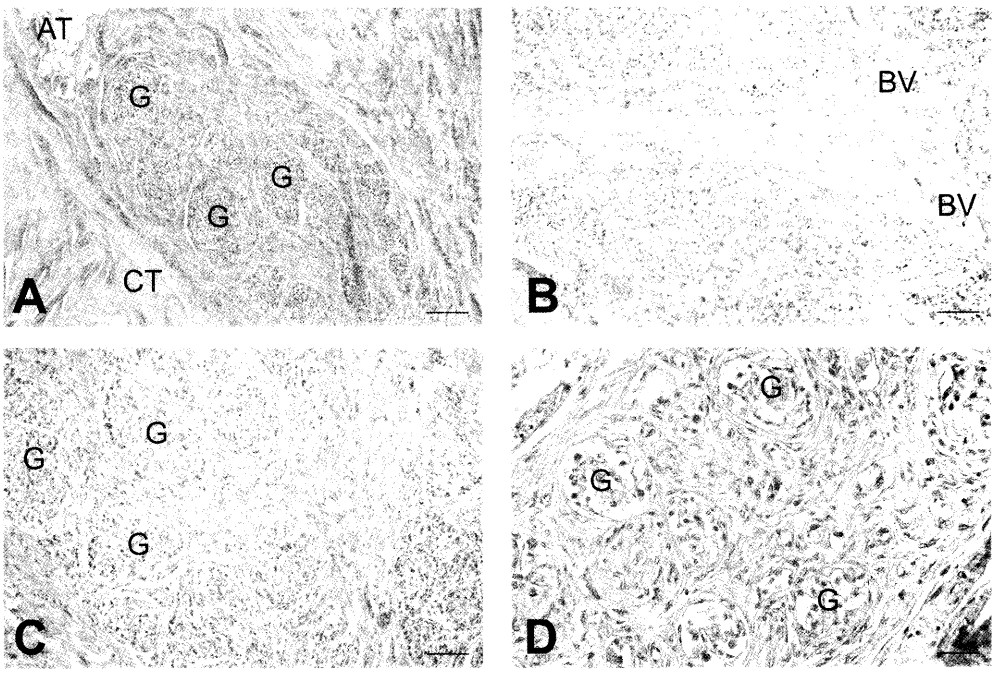

Fig. 1. Morphology of the human carotid body. (**A**) A conventional H&E staining showing the structural organization of the organ. Note the clusters, glomeruli (G) of parenchymal cells, the surrounding connective tissue (CT) and the adipose tissue located in the interlobular stroma. (**B**) A dense network of blood vessels (BV) is also dispersed in the stromal CT. (**C**) Juvenile human carotid body with compact glomic lobules (G) separated by thin septa of CT. (**D**) shows the carotid body of an elderly person. Note the denser and more compressed glomeruli (G) with progressive cellular degeneration. Scale bars = 200 μm (**A-C**); 50 μm (**D**).

pearance of the organ (Fig. 1B). The glomus cells are dually innervated by sensory and autonomic nerve fibers. Sensory innervation is provided by the carotid sinus nerve (also known as Hering's nerve), a branch of the glossopharyngeal nerve, while the sympathetic supply is provided by postganglionic neurons from the closely located superior cervical ganglion.

The principal cell type, the neuron-like type I or glomus cell, is considered to be the chemosensory cell of the organ [5, 19]. The glomus cells are round to oval in shape with a diameter of 10-16 μm and contain a large round, euchromatic nucleus and an abundant pale cytoplasm with numerous organelles. Amongst them, most notable are dense-cored secretory granules packed with putative neurotransmitters. Although smaller in size, they closely resemble the granules of paraneurons belonging to the diffuse neuroendocrine system cell family [13]. On the basis of the size and staining properties of their dense-cored vesicles, De Castro (1926) classically distinguished two types of glomus cells in the human CB: light and dark gomus cells [3]. Type II or sustentacular cells (~15-20% of all parenchymal cells) are glial-like supporting cells typically located at the periphery of the cell cluster. They are elongated cells with a disk-shaped hyperchromic nucleus and long cytoplasmic processes that partially envelop the glomus cells. Their cytoplasm lacks secretory granules but expresses glial marker enzymes such as the S-100 protein and glial fibrillary acidic protein [15]. Recently they have been assumed to be the stem cells in the adult CB [15].

The CB undergoes morphological changes with age. In general, it is best developed in children and young people [10], in which the characteristic cell clusters are more compact, separated by thin walls of connective tissue filled with a large number of fine blood vessels and nerve fibers (Fig. 1C). Aging leads to a decrease in the number of nerve fibers and glomus cells with a progressive cellular degeneration and an apparent increase in the surrounding connective tissue (Fig. 1D) [10, 17]. The organ also undergoes postmortal alterations, mostly associated with the nuclear morphology. Based upon differences in it, three distinct forms of glomus cells can be recognized in human glomic tissue: light, dark and pyknotic variants, the latter two representing postmortem changes [6, 18].

Neurochemistry of the human carotid body

A variety of neurochemical agents, both classical transmitters and neuropeptides, have been proposed to play a role in the chemosensory function [5, 9, 14]. Amongst them, the biogenic amines, including acetylcholine, norepinephrine, dopamine (Fig. 2A) and serotonin, represent the largest group in the human CB. In recent years, histamine has also been considered a putative transmitter in hypoxic chemosensitivity in humans (Fig. 2B) [10]. Other neuroactive substances such as some neuropeptides (substance P, VIP and enkephalins) and the gaseous neuromessengers nitric oxide and carbon monoxide also play a role as neuromodulators or second messengers, respectively, in oxygen sensing in the mammalian CB [16]. In their turn, the neurotransmitters contribute to the modulation of glomus cell function via autoreceptors as well.

Hypoxia-induced morphological and neurochemical plasticity of the human carotid body

There is convincing evidence that chronic hypoxia induces gene expression, leading to profound morphological changes in the human CB. In particular, long term hypoxic

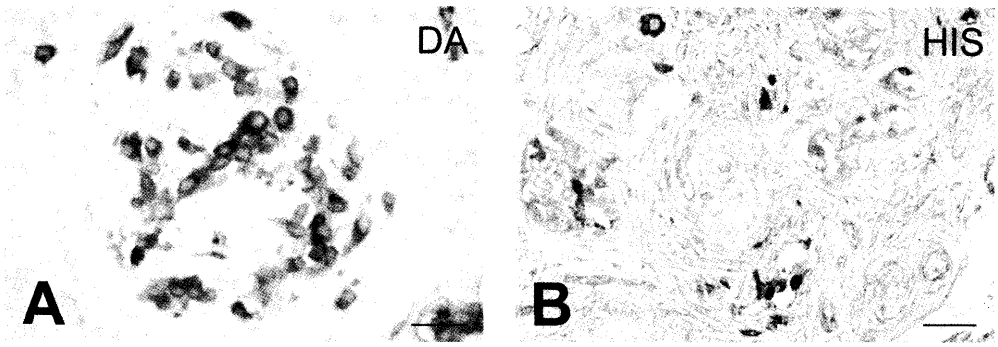

Fig. 2. Neurotransmitter traits in the human carotid body. (**A**) Immunohistochemical staining for dopamine (DA) in the mature carotid body. A subset of glomus cells is intensely immunostained. (**B**) A number of glomus cells exhibit strong immunoreactivity for histamine (HIS) in the adult carotid body. Scale bars = 25 μm (**A**); 50 μm (**B**).

exposure enlarges the CB, causing hypertrophy and mitosis of glomus cells, vasodilatation of the existing and growth of new blood vessels [20]. Such a physiological adaptive response to prolonged hypoxia occurs during acclimatization to high altitudes, or pathologically in patients suffering from systemic hypertension and/or cardiopulmonary diseases with concomitant hypoxemia [1].

In addition, it is well established that hypoxia causes glomus cells to depolarize and release transmitters, which bind to autoreceptors expressed by type I cells or postsynaptic receptors on apposed chemoafferent nerve terminals [5]. The predominant excitatory transmitters synthesized and released by glomus cells in response to hypoxia are acetylcholine and adenosine triphosphate while dopamine has a primarily inhibitory role in hypoxic chemosensitivity [9, 10, 14]. Our recent data have also proved the modulatory role of histamine as an essential excitatory modulator of the chemoreceptor activity upon hypoxia in man.

Carotid body chemotransduction mechanisms in disease

During the early postnatal life, human infants seem to be particularly vulnerable to hypoxic and hypercapnic episodes during sleep and to changes in peripheral chemoreception. This results in altered chemosensitivity which may be one of the factors contributing to a higher incidence of sudden infant death syndrome (SIDS), a disease responsible for unexpected deaths in newborns. Indeed, smaller than usual in size CBs or abnormalities in their transmitter content have been reported in victims of SIDS [4] and in subjects with congenital central hypoventilation syndrome. Conversely, an abnormal enlargement of the CB, elevated catecholamine synthesis and hypersensitivity to hypoxia have been shown in patients with essential hypertension, congestive heart failure and obstructive sleep apnea syndrome. It is likely that the CB tends to maintain oxygen homeostasis by marked morphological and neurochemical changes, and thus acts as a defense entity preventing the progression of morbidity associated with these diseases.

The carotid body neurogenic niche and its clinical applicability to cell therapy

The CB is the first neurogenic center identified outside the CNS. Recent research has demonstrated that the glia-like sustentacular cells sustain physiologic neurogenesis in the adult CB and in response to physiological hypoxia can proliferate and differentiate into new glomus cells [15]. The newly born neuron-like glomus cells are highly dopaminergic and produce neurotrophic factors such as GDNF, BDNF and NT3. Given their dopaminergic nature and ability to synthesize neurotrophins, CB stem cells could potentially be applied in cell replacement therapies in Parkinson's disease and in the treatment of other neurodegenerative disorders [reviewed in 12].

Conclusion

For over a century it has been known that the CB in man has an intricate internal structure. Due to several decades of extensive study, we are now aware of its remarkable ability to release a broad variety of transmitter agents in response to different chemostimuli. This provides clues on its important role in the homeostatic maintenance of the whole organism. Recent advances in human CB research and in understanding morphological and physiological mechanisms that operate in it have revealed that its histological structure and neurochemical profile alter upon hypoxia and certain cardiorespiratory disorders thus adapting the living organism to changing environmental or pathological conditions. Last but not least, the CB is a neurogenic center with a recognizable physiological role in adult life and, therefore, the cultivation of adult human CB progenitors in vitro should be a major task in future experimental work. Consequently, stem cell-derived glomus cells would enable successful autotransplantation of CB cell aggregates for tissue repair after injury or in neurodegenerative diseases.

References

1. Arias-Stell, J., J. Valcarcel. Chief cell hyperplasia in the human carotid body at high altitudes; physiologic and pathologic significance. – Hum. Pathol., 7, 1976, 361-373.
2. Atanasova, D. Y., M. E. Iliev, N. E. Lazarov. Morphology of the rat carotid body. – Biomed. Rev., 22, 2011, 41-55.
3. De Castro, F. Sur la structure et l'innervation de la glande intercarotidienne (glomus caroticum) de l'homme et des mammifères, et sur un noveau système d'innervation autonome du nerf glossopharyngien. – Trab. Lab. Invest. Biol. Univ. Madrid, 24, 1926, 365-432.
4. Gauda, E. B, E. Cristofalo, J. Nunez. Peripheral arterial chemoreceptors and sudden infant death syndrome. – Resp. Physiol. Neurobiol., 157, 2007, 162-170.
5. Gonzalez, C., L. Almaraz, A. Obeso, R. Rigual. Carotid body chemoreceptors: from natural stimuli to sensory discharges. – Physiol. Rev., 74, 1994, 829-898.
6. Heath, D., C. Edwards, P. Harris. Post-mortem size and structure of the human carotid body. Its relation to pulmonary disease and cardiac hypertrophy. – Thorax, 25, 1970, 129-140.
7. Heath, D., P. Lowe, P. Smith. Mast cells in the human carotid body. – J. Clin. Pathol., 40, 1987, 9-12.
8. Hempleman, S. C., S. J. Warburton. Comparative embryology of the carotid body. – Respir. Physiol. Neurobiol., 2012, http://dx.doi.org/10.1016/j.resp.2012.08.004.
9. Iturriaga, R., J. Alcayaga. Neurotransmission in the carotid body: transmitters and modulators between glomus cells and petrosal ganglion nerve terminals. – Brain Res. Rev., 47, 2004, 46-53.

10. Lazarov, N. E., S. Reindl, F. Fischer, M. Gratzl. Histaminergic and dopaminergic traits in the human carotid body. – Respir. Physiol. Neurobiol., 165, 2009, 131-136.
11. Lopez-Barneo, J. Oxygen and glucose sensing by carotid body glomus cells. – Curr. Opin. Neurobiol., 13, 2003, 493-499.
12. López-Barneo, J., R. Pardal, P. Ortega-Sáenz, R. Durán, J. Villadiego, J. J. Toledo-Aral. The neurogenic niche in the carotid body and its applicability to antiparkinsonian cell therapy. – J. Neural Transm., 116, 2009, 975-982.
13. McDonald, D. M. Peripheral chemoreceptors. Structure-function relationships of the carotid body. In: Regulation of breathing (Ed. T. F. Hornbein). New York, Dekker, 1981, 105-319.
14. Nurse, C. A. Neurotransmission and neuromodulation in the chemosensory carotid body. – Auton. Neurosci., 120, 2005, 1-9.
15. Pardal, R., P. Ortega-Sáenz, R. Durán, J. López-Barneo. Glia-like stem cells sustain physiologic neurogenesis in the adult mammalian carotid body. – Cell, 131, 2007, 364-377.
16. Prabhakar, N. R. Neurotransmitters in the carotid body. — Adv. Exp. Med. Biol., 360, 1994, 57-69.
17. Sarrat-Torres, M. A., A. Torres, J. Whyte, S. Baena, A. Cisneros, R. Sarrat. Structure, location, function and pathological features of the human carotid body. – Eur. J. Anat., 10, 2006, 1-5.
18. Seker, M., D. J. Pallot, J.-O. Habeck, A. Abramovici. Postmortem changes in the human carotid body. In: Arterial chemoreceptors: cell to system (Eds. R. G. O'Regan, P. Nolan, D. S. McQueen, D. J. Paterson). New York, Plenum Press, 1994, 349-351.
19. Verna, A. The mammalian carotid body: morphological data. In: The carotid body chemoreceptors (Ed. C. Gonzalez). Austin, Landes Bioscience, 1997, 1-29.
20. Wang, Z. Y., G. E. Bisgard. Chronic hypoxia-induced morphological and neurochemical changes in the carotid body. – Misrosc. Res. Tech., 59, 2002; 168-177.