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Review

Oxygen-sensing by arterial chemoreceptors: Mechanisms and medical translation

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ABSTRACT

Acute O_2 sensing is necessary for the activation of cardiorespiratory reflexes (hyperventilation and sympathetic activation), which permit the survival of individuals under hypoxic environments (e.g. high altitude) or medical conditions presenting with reduced capacity for gas exchange between the lung alveoli and the blood. Changes in blood O_2 tension are detected by the arterial chemoreceptors, in particular the carotid body (CB), which act in concert with the adrenal medulla (AM) to facilitate rapid adaptations to hypoxia. The field of arterial chemoreception has undergone a considerable expansion in recent years, with many of the fundamental observations made at the molecular and cellular levels serving to improve our understanding of the pathogenesis of numerous medical disorders, and even to propose advances in the treatment strategies. In this review, after a short historical preface, we describe the current model of chemosensory transduction based on the modulation of membrane K^+ channels by O_2 in specialized chemoreceptor cells. Recent progress in elucidating the molecular mechanisms underlying the modulation of ion channels by O_2 tension, which involves mitochondrial complex I, is also discussed. The discovery in the last few years of a specific population of neural crest-derived stem cells in the CB explains the reversible growth of this organ, an intriguing and unusual property of this type of neuronal tissue that contributes to acclimatization under chronic hypoxia. The essential homeostatic role of the CB-AM axis is clearly evident in newly generated mouse models that reach adulthood, albeit with CB and AM atrophy. These animals exhibit a marked intolerance to even mild hypoxia. CB inhibition or over-activation can have important medical consequences. Respiratory depression by general anesthetics or by opioid use is a common clinical condition that frequently causes death in susceptible individuals. An exaggerated sympathetic outflow due to over-activation of the CB-AM axis may contribute to the pathogenesis of several highly prevalent medical conditions, such as chronic heart failure, obstructive sleep apnea, obesity, metabolic syndrome, and diabetes. A detailed understanding of the molecular mechanisms underlying acute O_2 sensing may help in the design of more efficient therapeutic approaches to combat these disorders.

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1. Introduction

An appreciation of the reflex activation of the arterial chemoreceptors by a decrease in the level of oxygen (O_2) tension in the blood (hypoxemia) represents a classical chapter in medical physiology. The provision of sufficient O_2 to the tissues is a fundamental physiological challenge as O_2 is necessary for oxidative metabolism, with even a transient lack of O_2 (hypoxia) playing a critical role in the pathogenesis of a number of major causes of morbidity and mortality. In the last two decades, we have witnessed significant progress in our knowledge of the adaptive responses to hypoxia by cells and organisms. In addition to the activation of arterial chemoreceptors, which in a few seconds induces hyperventilation and sympathetic activation to increase the uptake of O_2 and its distribution to the tissues (López-Barneo et al., 2001), hypoxia activates a powerful and generalized genetic program, due to the induction of the prolyl hydroxylase (PHD)-hypoxia inducible factor (HIF) pathway. Over the course of hours or days, HIF-dependent genes cause a cellular switch to predominantly non-aerobic metabolism and an increase in the number of O_2-transporting red blood cells and blood vessels (Brahimi-Horn and Pouyssegur, 2007; Kaelin and Ratcliffe, 2008; Semenza, 2014). This article focuses on the acute responses to hypoxia mediated by specialized O_2-sensitive cells in the arterial chemoreceptors which, together with other organs, comprise the homeostatic oxygen-sensing system (Weir et al., 2005). The principal arterial chemoreceptor is the carotid body (CB), a paired organ located at the bifurcation of the carotid arteries that contains O_2-sensitive, neuron-like, glomus cells innervated by sensory fibers connected to the respiratory center (López-Barneo et al., 2001). The CB chemoreflex protects against hypoxemia, as well as contributing to the eupneic drive to breathe (Dahan et al., 2007) and the control of blood flow during exercise (Dempsey, 2012). The CB acts in concert with the adrenal medulla (AM) to modulate sympathetic tone under hypoxia, although AM cells also have some intrinsic O_2 sensitivity, particularly in the neonate (Cheung, 1989; Seidler and Slotkin, 1985). In addition to their critical minute-to-minute regulatory actions on the respiratory and cardiovascular systems, the arterial chemoreceptors, in particular the CB, have a fundamental role in acclimatization to hypoxemia (or low O_2 tension -PO_2- in the blood), a condition that frequently affects people who live at or travel to high altitudes (Joseph and Pequignot, 2009; Wilson et al., 2009) and patients with chronic pulmonary diseases that reduce the O_2 exchange capacity between the air and the pulmonary capillaries (Schou et al., 2012).

Although it is almost 100 years since the field of arterial chemoreception was founded, it has only been during the last few decades, and particularly in recent years, that fundamental aspects of cell responsiveness to hypoxia have begun to be elucidated. Here, after a brief historical preface, we summarize the progress that has taken place in our understanding of the physiology of O_2-sensitive CB and AM cells, with an emphasis on recent advances in relation to the molecular mechanism of acute O_2 sensing and the properties of CB adult stem cells that support CB plasticity during acclimatization to hypoxia. Finally, we will deal with the exciting and rapidly expanding translational research related to the participation of the CB-AM axis in the pathogenesis of highly prevalent human medical conditions and diseases.

2. Origins of arterial chemoreception

By the beginning of the 20th century, several investigators had already proposed that the carotid region was the origin of acute cardiorespiratory reflexes that cause changes in ventilation and heart rate. However, it was Heinrich Hering (1924) who first demonstrated that electrical or mechanical stimulation of the carotid sinus (a dilated area near the carotid bifurcation) triggers a reflex (the "sinus reflex") that provokes bradycardia and arterial hypotension. Indeed, this German physiologist discovered that the carotid region is innervated by a branch of the glossopharyngeal nerve designated the "sinus or Hering's nerve". Around the same time, the Belgian group led by Jean-François Heymans and his son Corneille also suggested that the cardio-aortic region has a major role in the regulation of respiration which is conditioned by the pressure and composition of the circulating blood (Heymans and Heymans, 1927). It was, however, Fernando de Castro, a young Spanish anatomist and pupil of Santiago Ramón y Cajal, who carried out a seminal study on the separate innervation of the carotid sinus (baroreceptor) and the CB, which led him to propose, based on the rich irrigation and sensory innervation of the latter organ (at that time called the *glomus caroticum*), that it was a chemoreceptor that "tasted" the chemical composition of the blood and represented the origin of respiratory reflexes (de Castro, 1926, 1928). In a series of elegant studies, Corneille Heymans and co-workers demonstrated that the CB is indeed the origin of respiratory reflexes induced by hypoxemia,

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