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Review

Oxygen sensing in the body

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Abstract

This review is divided into three parts: (a) The primary site of oxygen sensing is the carotid body which instantaneously respond to hypoxia without involving new protein synthesis, and is historically known as the first oxygen sensor and is therefore placed in the first section (Lahiri, Roy, Baby and Hoshi). The carotid body senses oxygen in acute hypoxia, and produces appropriate responses such as increases in breathing, replenishing oxygen from air. How this oxygen is sensed at a relatively high level (arterial $P_{O_2} \simeq 50$ Torr) which would not be perceptible by other cells in the body, is a mystery. This response is seen in afferent nerves which are connected synaptically to type I or glomus cells of the carotid body. The major effect of oxygen sensing is the increase in cytosolic calcium, ultimately by influx from extracellular calcium whose concentration is 2×10^4 times greater. There are several contesting hypotheses for this response: one, the mitochondrial hypothesis which states that the electron transport from the substrate to oxygen through the respiratory chain is retarded as the oxygen pressure falls, and the mitochondrial membrane is depolarized leading to the calcium release from the complex of mitochondria–endoplasmic reticulum. This is followed by influx of calcium. Also, the inhibitors of the respiratory chain result in mitochondrial depolarization and calcium release. The other hypothesis (membrane model) states that K^+ channels are suppressed by hypoxia which depolarizes the membrane leading to calcium influx and cytosolic calcium increase. Evidence supports both the hypotheses. Hypoxia also inhibits prolyl hydroxylases which are present in all the cells. This inhibition results in membrane K^+ current suppression which is followed by cell depolarization. The theme of this section covers first what and where the oxygen sensors are; second, what

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are the effectors; third, what couples oxygen sensors and the effectors. (b) All oxygen consuming cells have a built-in mechanism, the transcription factor HIF-1, the discovery of which has led to the delineation of oxygen-regulated gene expression. This response to chronic hypoxia needs new protein synthesis, and the proteins of these genes mediate the adaptive physiological responses. HIF-1α, which is a part of HIF-1, has come to be known as master regulator for oxygen homeostasis, and is precisely regulated by the cellular oxygen concentration. Thus, the HIF-1 encompasses the chronic responses (gene expression in all cells of the body). The molecular biology of oxygen sensing is reviewed in this section (Semenza). (c) Once oxygen is sensed and Ca^{2+} is released, the neurotransmittesr will be elaborated from the glomus cells of the carotid body. Currently it is believed that hypoxia facilitates release of one or more excitatory transmitters from glomus cells, which by depolarizing the nearby afferent terminals, leads to increases in the sensory discharge. The transmitters expressed in the carotid body can be classified into two major categories: conventional and unconventional. The conventional neurotransmitters include those stored in synaptic vesicles and mediate their action via activation of specific membrane bound receptors often coupled to G-proteins. Unconventional neurotransmitters are those that are not stored in synaptic vesicles, but spontaneously generated by enzymatic reactions and exert their biological responses either by interacting with cytosolic enzymes or by direct modifications of proteins. The gas molecules such as NO and CO belong to this latter category of neurotransmitters and have unique functions. Co-localization and co-release of neurotransmitters have also been described. Often interactions between excitatory and inhibitory messenger molecules also occur. Carotid body contains all kinds of transmitters, and an interplay between them must occur. But very little has come to be known as yet. Glimpses of these interactions are evident in the discussion in the last section (Prabhakar).

Keywords: Action spectra; α-ketoglutarate; Chronic hypoxia; Capacitative Ca^{2+} influx; Endogenous gas molecules-NO and CO messenger molecules; ER-mitochondria Ca^{2+} liaison; Glomus cell and nerve junction; Fe^{2+} chelation; HIF-1α; HIF-1β; HIF-1; Heme nature of O_2 sensor; Hydroxylation; Intermittent hypoxia; IP_3-Rs Membrane model; O_2 sensitive K^+ channels; Mitochondrial model; Mitochondria-HIF-1α; Molecular biology of oxygen sensing; Prolyl hydroxylase inhibitors; Neurotransmitters: conventional and unconventional; ROS; Spatial localization of mitochondria; Sustained hypoxia; TEA and 4-AP effects; Ventilation

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