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Review

Oxygen sensing and metabolic homeostasis

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ABSTRACT

Oxygen-sensing mechanisms have evolved to maintain cell and tissue homeostasis since the ability to sense and respond to changes in oxygen is essential for survival. The primary site of oxygen sensing occurs at the level of the carotid body which in response to hypoxia signals increased ventilation without the need for new protein synthesis. Chronic hypoxia activates cellular sensing mechanisms which lead to protein synthesis designed to alter cellular metabolism so cells can adapt to the low oxygen environment without suffering toxicity. The master regulator of the cellular response is hypoxia-inducible factor (HIF). Activation of this system under condition of hypobaric hypoxia leads to weight loss accompanied by increased basal metabolic rate and suppression of appetite. These effects are dose dependent, gender and genetic specific, and results in adverse effects if the exposure is extreme. Hypoxic adipose tissue may represent a unified cellular mechanism for variety of metabolic disorders, and insulin resistance in patients with metabolic syndrome.

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1. Introduction

Oxygen is a vital metabolic substrate for cellular functions. Oxygen sensing occurs at many levels and is critical for successful adaption to abnormal oxygen levels due either to changes in ambient oxygen levels or because of disease processes. A global oxygen sensing mechanism is represented by the ability of the glomus cells in the carotid body to signal increased ventilation in response to hypoxemia. When an imbalance between oxygen supply and demand results in hypoxemia a cascade of physiologic and biochemical events is triggered potentially resulting in deleterious effects on enzyme activities, mitochondrial function, cytoskeletal structure, and membrane transport. At the cellular level adaptation to hypoxia is an essential cellular response controlled by the oxygen-sensitive transcription factor hypoxia-inducible factor 1 (HIF-1). Studies in normal subjects exposed to hypoxia at altitude illustrate the metabolic consequences of HIF activation. At altitude hypoxia results from the reduction in barometric pressure causing a decrease in the in-

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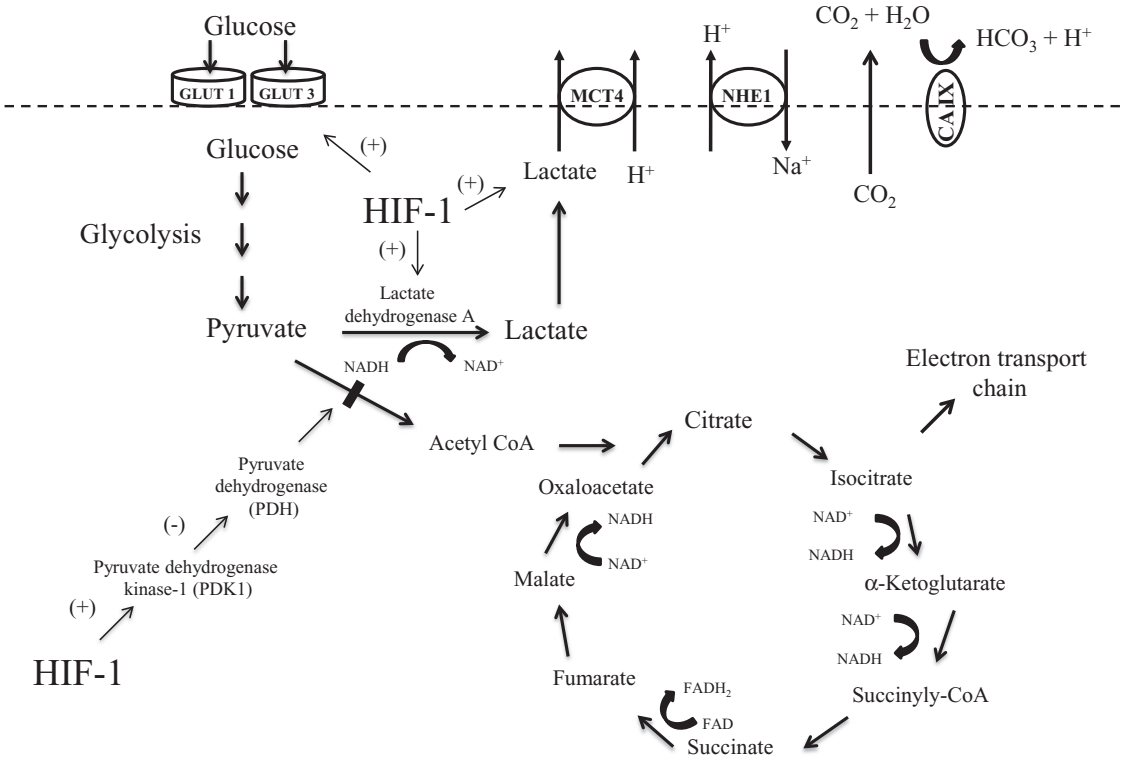

Fig. 1. Under condition of limited oxygen supply upregulation of hypoxia inducible factor leads to a shift in cell metabolism favoring glycolysis so as to limit generation of potentially harmful reactive oxygen species via oxidative phosphorylation in the mitochondria. A critical step in this shift is HIF-mediated activation of pyruvate dehydrogenase kinase-1 (PDK-1). This enzyme inactivates pyruvate dehydrogenase which is the mitochondrial enzyme responsible for converting pyruvate to acetyl-CoA. In combination with activation of lactate dehydrogenase A (LDHA) which converts pyruvate to lactate, there is less delivery of acetyl-CoA into the Krebs cycle and therefore a reduction of flavin adenine dinucleotide (FADH2) and nicotinamide adenine dinucleotide (NADH) delivered to the electron transport chain. HIF upregulates the expression of GLUT1 and GLUT3 on the cell membrane so as to facilitate glucose entry into the cell. HIF also upregulates monocarboxylate transporter 4 which is a proton-lactate symporter. This transporter creates an avenue for lactate exit from the cell. The cotransport of the proton contributes to the maintenance of intracellular pH. Cell pH is also defended by HIF-induced expression of carbonic anhydrase-9 and increased expression of the Na^+/H^+ antiporter, NHE1.

spired partial pressure of oxygen. This paper will focus on the cellular response to hypoxemia giving particular emphasis to how HIF activation alters metabolic homeostasis in both favorable as well as unfavorable ways depending on the cause and duration of hypoxemia.

2. Hypoxia inducible factor

HIF is a DNA-binding transcription factor which in association with specific nuclear cofactors transactivates a variety of genes triggering an adaptive response aimed to optimize the utilization of available oxygen under conditions of hypoxia (Greer et al., 2012; Semenza, 2012). The three members of the family (HIF-1, HIF-2 and HIF-3) are heterodimers consisting of an oxygen-sensitive α-subunit and a constitutively expressed β-subunit. In the presence of oxygen, HIFα is extremely unstable due to an oxygen-dependent hydroxylation which targets it for proteosomal degradation. This hydroxylation is mediated by three prolyl hydroxylases (PHD1-3) and requires oxygen as well as Fe^{2+}, 2-oxoglutarate, and ascorbate for their catalytic activity (Appelhoff et al., 2004). Prolyl-hydroxylated HIFα is bound by the von Hippel-Lindau (VHL) tumor suppressor protein and subsequently ubiquitylated by the elongin C–elongin B–cullin 2–E3-ubiquitin–ligase complex marking HIFα for proteosomal degradation. The requirement of oxygen for the catalytic activity of PHD1-3 allows for HIFα to escape recognition by VHL under conditions of hypoxia. In this setting HIFα is stabilized and accumulates in the nucleus where it dimerizes with HIFβ and subsequently binds to the hypoxia response element in target genes.

Activation of HIF-induced genes give rise to a myriad of effects designed to promote survival in low-oxygen conditions. These include increases in red cell mass brought about by stimulation of erythropoietin production and promotion of angiogenesis through stimulation of vascular endothelial growth factor (VEGF). HIF-induced gene activation also causes a coordinated shift in metabolism from oxidative phosphorylation to a less oxygen requiring production of ATP via the glycolytic pathway (Hamanaka and Chandel, 2010) (Fig. 1). A critical step in this shift is HIF-mediated activation of pyruvate dehydrogenase kinase-1 (PDK-1). This enzyme inactivates pyruvate dehydrogenase which is the mitochondrial enzyme responsible for converting pyruvate to acetyl-CoA. In combination with activation of lactate dehydrogenase A (LDHA) which converts pyruvate to lactate, there is less delivery of acetyl-CoA into the Krebs cycle and therefore a reduction of flavin adenine dinucleotide (FADH2) and nicotinamide adenine dinucleotide (NADH) delivered to the electron transport chain. This shift away from mitochondrial respiration serves to reduce the production of potentially harmful reactive oxygen species which occurs as a function of decreasing oxygen tension (Wheaton and Chandel, 2011).

Under normoxic conditions reduction of molecular oxygen to water by the mitochondrial electron transport chain enables the conversion of ADP into ATP providing the energy source for normal cellular function. In this setting generation of reactive oxygen species (ROS) is minimal (Turrens, 2003). When oxygen becomes limiting, however, there is increased production of ROS which can lead to cellular damage and dysfunction. Increased production of ROS is the result of electrons being delivered to oxygen prior to the reduc-