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REVIEW

Hypoxia, vascular smooth muscles and endothelium

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Abstract Hypoxia, or the lack of oxygen, has multiple impacts on the vascular system. The major molecular sensors for hypoxia at the cellular level are hypoxia inducible factor and heme oxygenase. Hypoxia also acts on the vasculature directly conveying its damaging effects through disruption of the control of vascular tone, particularly in the coronary circulation, enhancement of inflammatory responses and activation of coagulation pathways. These effects could be particularly detrimental under pathological conditions such as obstructive sleep apnea and other breathing disorders.

Abbreviations: cADPR, cyclic adenosine diphosphoribose; cGMP, cyclic guanosine monophosphate; EDCF, endothelium derived contracting factor; eNOS, endothelial nitric oxide synthase; ET, endothelin; GMP, guanine monophosphate; HIF, hypoxia inducible factor; HO, heme oxygenase; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemotatic protein-1; mRNA, messenger ribose nucleic acid; mTOR, mammalian target of rapamycin; NADH, nicotinamide adenine dinucleotide; NO, nitric oxide; NOX, NADPH oxidase; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase; VCAM-1, vascular cell adhesion molecule-1

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1. Introduction

Hypoxia is the term describing a state of lack of oxygen endangering cell function. This condition can occur in four main ways: (1) Hypoxic hypoxia, caused by an insufficient oxygen concentration in the air in the lungs, which is common during sleep apnea, when the diffusion of oxygen to the blood is reduced or in high altitude sickness; (2) Hypoxemic hypoxia, occurring when the blood has reduced transport capacity as seen in carbon monoxide poisoning when hemoglobin cannot carry as much oxygen; (3) Stagnant hypoxia results when the cardiac output does not match the demands of the body and the flow is not sufficient to deliver enough oxygenated blood to the tissue; and (4) Histotoxic hypoxia, when the cells cannot utilize the available oxygen, for example during cyanide poisoning when oxygen cannot be used to produce ATP as the mitochondrial electron transport is inhibited[1]. Whatever the cause, a reduction in oxygen concentration in the arterial blood will trigger the chemoreceptors of the carotid body and initiate a major activation of the sympathetic system; this causes pronounced vasoconstriction throughout the body, and can lead to a rapid rise in arterial blood pressure[2–5]. A local shortage in oxygen supply also sets in motion a number of immediate local (as opposed to reflex) changes leading to vasoconstriction and vasodilatation which involve both endothelial and vascular smooth muscle cells.

2. Oxygen sensing

The sensor(s) responsible for the acute vascular response to hypoxia is/are elusive. In endothelial cells, hypoxia can destabilize eNOS mRNA by a mechanism involving Rho kinase[6]. Oxidation of tetrahydrobiopterin, a co-factor of eNOS, promotes ROS production by eNOS[7,8]. At the level of the vascular smooth muscle, the production of reactive oxygen species (ROS) during hypoxia will attenuate relaxations to nitric oxide, as ROS scavenge NO[9,10]. For more long-term effects of hypoxia on the vascular wall, major players appear to be heme oxygenase (HO) and hypoxia inducible factor (HIF).

2.1. Reactive oxygen species

ROS may be signaling molecules during the response to hypoxia. During the latter, the mitochondrial complex III produces ROS[11,12]. In addition, NADPH oxidase (NOX), which belongs to a class of proteins that transfer electrons across membranes[13], underlies the increase of ROS during hypoxia[14]. The ROS level changes upon exposure to hypoxia[15,16], this change may modulate the activity of several targets to cause either relaxations or contractions, including soluble guanylyl cyclase (sGC)[17], potassium and calcium channels (such as sarcoplasmic reticulum calcium ATPase)[18,19]. ROS can also stabilize hypoxia inducible factors by inhibiting prolyl hydroxylase[20,21].

There are number of potential sources that generate ROS, among which the isoforms of NAD(P)H oxidase, which contain a subunit with a flavin system transferring electrons to cytochrome b_{558}[22]. In smooth muscles of bovine large and resistance arteries, hypoxia increases the superoxide anion level, a response inhibited by diphenylene iodonium (NOX inhibitor)[23]. The latter drug also attenuates the hypoxic response in the pulmonary artery of cats[23]. Another major source of ROS is the electron transport chain of the mitochondria, in which the NADH dehydrogenase of complex I and the *Q* cycle of complex III are sensitive to rotenone and myxothiazole, respectively. These agents attenuate the increased ROS generation stimulated by hypoxia in cultured rat pulmonary arterial smooth muscles and reduce the hypoxia-elicited vasoconstriction in perfused rat lungs[24,25]. Other enzymes that can produce ROS include xanthine oxidase[26], cytochrome P-450[27], cyclooxygenase[28] and nitric oxide synthase[29].

2.2. Heme oxygenase

HO is responsible for the breakdown of heme. Three isoforms of this enzyme have been identified. HO-1 is the inducible isoform, with anti-atherosclerotic and anti-myotrophic properties[30]. HO-2 is expressed constitutively in most tissues[31]; in the mouse, its deletion results in impaired immunity, abnormal oxygen sensing and ejaculatory abnormalities[32]. HO-3 is expressed in several tissues but its function is less well characterized[31,33,34]. Hypoxemia enhances the expression of HO-1[35,36]. The enzyme is tightly associated with large conductance calcium activated potassium channel (BK_{Ca}) in the carotid body and its activation in response to hypoxia causes depolarization in the glomus cells[37], implying a modulatory role in reflex chemoreception. By contrast, in HO-2 knockout mice, the oxygen sensing ability of the carotid body is not affected significantly[38].

In all tissues, HO-1 and HO-2 release carbon monoxide and iron during the metabolism of heme[39,40]. Carbon monoxide can in turn activate sGC leading to the production of cyclic guanosine monophosphate (cGMP) and relaxation of vascular smooth muscle[41]. The level of activity of HO-1 helps to regulate vascular tone. Thus, up-regulation of HO-1 reduces arterial blood pressure and prevents endothelial dysfunction in the spontaneous hypertensive rat[42].

2.3. Hypoxia inducible factor

More prolonged effects, especially at the genomic level, of hypoxia depend on the over-expression of HIF, a dimer consisting of α and β subunits[43]. The α subunit is expressed constitutively but it is susceptible of oxygen-dependent post-translational modifications. When the oxygen supply is sufficient (normoxia), HIF is hydroxylated by prolyl-hydroxylase and degraded through an ubiquitin-dependent pathway[43,44]. Prolyl-hydroxylase is inactivated when oxygen is insufficient, resulting in HIF accumulation in the cells. This mechanism explains the oxygen sensing ability of the factor[44]. There are three isoforms of the α subunit, HIF-1α, HIF-2α and HIF-3α. When not degraded, HIF-1α binds to HIF-1β and activates a number of genes. HIF is a powerful transcription factor and promotes transcription of genes associated with angiogenesis (vascular endothelial growth factors)[45] and metalloproteinases[46] and metabolism (glucose transporter 1)[43]. HIF-2α is responsible for erythropoietin production in response to hypoxia[47]. HIF-3α is not well characterized but is more abundant in tissues such as lung epithelial cells[48].