Hypoxia, coronary dilation, and the pentose phosphate pathway

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Hypoxic vasorelaxation of resistance arteries is an important feedback control mechanism to maintain adequate oxygenation of metabolically active tissues and is essential in tissues where oxygen extraction is nearly maximized, as it is in the heart. Although the physiological importance of this response has been appreciated for decades, the underlying cellular and molecular mechanisms remain incompletely understood.

Under conditions of low arterial PO2, a number of factors act to match coronary blood flow with oxygen consumption (Fig. 1). The hypoxic environment elicits neural stimuli and release of humoral substances from adjacent cardiac tissue that stimulate vasodilation. Adenosine, potassium ions, hydrogen ions, and sympathetic activation can all contribute to dilation during hypoxia (1, 10). However, these factors do not fully account for hypoxic dilation (17) and do not address the direct relaxing effect of hypoxia on isolated vessels. This is important because, in contrast to metabolic regulation of vasomotor tone, it is important for hypoxia to elicit a direct vasodilator response from cardiac resistance vessels. Systemic vessels are intrinsically sensitive to changes in PO2, and identification of the vascular oxygen sensor has been the subject of intense investigation. In recent studies, intracellular reactive oxygen species (ROS)-generating systems including NAD(P)H oxidase (7, 20) and the mitochondrial electron transport chain (9, 18) have been implicated as vascular oxygen sensors (16).

As reported in this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Gupte and Wolin (5) have identified a novel mechanism whereby hypoxia induces relaxation of the isolated, endothelium-denuded coronary artery (BCA) by decreasing NADPH and glutathione (GSH) concentrations in the vascular smooth muscle. This new mechanism nicely links two prior observations made by the same group. First, hypoxia relaxes BCA by a mechanism that does not appear to involve a release of endothelial nitric oxide or prostaglandins or changes in ROS (12). Second, relaxation of the BCA to pentose phosphate pathway (PPP) inhibitors involves decreased NADPH and GSH and reduced intracellular calcium (3). The present study links hypoxia-induced relaxation with inhibition of the PPP by showing that hypoxic vasodilation is associated with reduced flux through the PPP, decreased cytosolic NADPH, decreased Ca2+, influx, and accelerated activity of the sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA) pump. Modulation of this pathway implicates PPP inhibition as an intrinsic mechanism of hypoxic dilation. Although the specific molecular mechanism underlying this effect of low PO2 on the PPP remains unclear, it may involve a hypoxia-induced depletion of glucose-6-phosphate, the substrate for the rate-limiting enzyme of the PPP, that then promotes the accumulation of NADP+ and the depletion of NADPH.

The PPP is an important modulator of the overall redox state of the cell through reduction of NADP+ to NADPH, a key cofactor for several cellular enzymes. Flux through this pathway may regulate a number of redox-sensitive cellular targets that affect vasomotor function, including soluble guanylyl cyclase, potassium channels, and the SERCA pump (3, 19). The present report (5) provides evidence that hypoxia may indirectly modulate the activity of the SERCA pump via an effect on the PPP to lower intracellular calcium. Importantly, this effect on the PPP occurs in the absence of alterations in cellular ATP, suggesting that hypoxia-induced relaxation of the BCA is independent of alterations in mitochondrial energy metabolism. This response may therefore represent an important initial feedback mechanism under conditions of mild to moderate hypoxia, whereby blood flow is increased, tissue PO2 is restored, and mitochondrial impairment is prevented.

The endothelium plays a prominent regulatory role in many aspects of vascular biology by functioning as a sensor for neurotransmitters and hormones, such as acetylcholine, bradykinin, or angiotensin II, or as a sensor for shear stress across its luminal surface. The endothelium transduces these signals to the underlying muscle layer by releasing vasoactive constricting or relaxing factors. These factors modulate vasomotor tone and local tissue perfusion. In the isolated BCA, Gupte and Wolin (5) report that hypoxia promotes relaxation in the absence of the endothelium. This is consistent with a previous study from this laboratory (12) showing that hypoxic vasorelaxation of the BCA is not mediated by NO or prostaglandins and is not altered by endothelial denudation. Other reports confirm that hypoxic vasorelaxation can occur in isolated vessels in the absence of a functional endothelium (2, 15). Although the endothelium is not required for hypoxic vasorelaxation of the BCA in vitro, this cell layer is also sensitive to changes in PO2 and may release vasoactive metabolites that could potentially contribute to the functional response to hypoxia in vivo (2, 14). In any case, a vascular smooth muscle-specific oxygen sensor may be particularly important in cardiovascular disease when the endothelium is dysfunctional, and should therefore be studied in greater depth.

An interesting finding of the present study (5) is that hypoxia promotes the oxidation of NADPH in the BCA, a redox phenomenon that is somewhat counterintuitive, as low PO2 is usually associated with reductive potential. The associated decrease in cellular NADPH is coupled with lower intracellular calcium, which probably initiates relaxation. However, an alternative explanation is that the decrease in NADPH may reduce NAD(P)H oxidase activity, thereby lowering superoxide and hydrogen peroxide generation by this enzyme. Because these ROS can inhibit potassium channels and other proteins involved in the mechanism of vasodilation (6), reduced ROS levels would be expected to facilitate vasorelaxation. Consis-
tent with this hypothesis, Wolin’s group (4) has shown that inhibition of the PPP reduces ROS generation in the bovine coronary vasculature. However, the situation is more complex. Previous reports from Wolin’s group (11, 12) indicate that hypoxic vasorelaxation of the BCA occurs without changes in ROS production. Thus, although the mechanism whereby hypoxia induces oxidation independent of ROS production remains unknown, it would be intriguing to examine whether apocynin, an inhibitor of NAD(P)H oxidase, alters hypoxic dilation in this model.

There are potential clinical ramifications of the study by Gupte and Wolin (5). They observed that hypoxic vasorelaxation is enhanced under glucose-free conditions and attenuated with addition of pyruvate, consistent with a sensitivity to the availability of substrate for the PPP. Although the inhibitory effects of hyperglycemia on endothelial function are well established and involve enhanced oxidative stress (13), the present study suggests that high glucose concentrations may also impair the intrinsic oxygen sensor in the vascular smooth muscle. This could have adverse effects in diabetic patients with cardiovascular disease, in which endothelium-mediated and endothelium-independent dilator mechanisms could be simultaneously impaired, possibly explaining the increased cardiovascular morbidity and mortality observed in diabetic patients. In contrast, it is interesting to speculate that subjects with the common biochemical absence of glucose-6-phosphate dehydrogenase may demonstrate a greater sensitivity to the vasodilator effects of hypoxia. Additional studies are needed to determine the physiological and pathological significance of the inhibitory effect of glucose on this particular mechanism in the broader context of vascular biology.

In conclusion, the present report by Gupte and Wolin (5) identifies the PPP as a novel oxygen sensor in the vascular smooth muscle that modulates hypoxic coronary vasodilation. This study expands our understanding of the complex mechanism underlying this fundamental physiological response of the vasculature to low PO2. Future studies are needed to determine the functional significance of this redox signaling pathway in various physiological and pathological conditions.

REFERENCES


