Inhibition of Prolyl Hydroxylase Domain-Containing Protein: A Novel Therapy for Cardiovascular Diseases?

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Intermittent hypoxia, such as that observed in patients with sleep apnea, is frequently associated with hypertension and other cardiovascular diseases. Hypoxia also participates in pathophysiological remodeling of cardiac myocytes, as well as remodeling of the vasculature. Overreactivity of the renin-angiotensin system (RAS) has long been implicated in the etiology of hypertension associated with hypoxia, and a recent human study confirms the importance of the angiotensin II type I (AT1) receptor activation in this process. However, current knowledge regarding the molecular mechanism by which RAS is activated and mediates cardiovascular diseases under hypoxia remains quite limited.

The cellular response to hypoxia involves the induction of the hypoxia-inducible factor 1α (HIF1α), considered to be the major transcription factor involved in gene regulation by hypoxia. In normoxia, HIF1α is hydroxylated by the cellular oxygen “sensor” prolyl-hydroxylase domain (PHD) proteins (PHD1, PHD2, and PHD3) and degraded by proteasomes. The PHDs are inhibited in hypoxia, resulting in stabilization and activation of transcription by the nonhydroxylated and stabilized form of HIF1α. PHDs are an evolutionarily conserved subfamily of dioxygenases that use oxygen and 2-oxoglutarate as cosubstrates and iron and ascorbate as cofactors. Cobalt (II) is known to inhibit PHDs by reducing intracellular ascorbate and cause HIF1α stabilization. Therefore, CoCl2 has been used as a PHD inhibitor and as a hypoxia mimetic. Known human mutations and knockout mouse approaches suggest PHD2 as the major enzyme regulating HIF1α in mammals.

In this issue of Hypertension, Matsuura et al4 have elucidated the role of PHD2 in regulating the expression of the AT1 receptor in cultured rat aortic vascular smooth muscle cells (VSMCs). Not only hypoxia and CoCl2 but also PHD2 small interfering RNA reduced AT1 receptor expression. Interestingly, although the AT1 receptor suppression appears to be regulated in part at a transcriptional level, it seems to be through an HIF1α-independent mechanism. Moreover, treatment with CoCl2 markedly reduced perivascular fibrosis in mouse heart induced by angiotensin II infusion. These novel findings will help to clarify the potential molecular mechanisms by which hypoxic conditions alter the tissue and circulating RAS components and thereby participate in the progression of cardiovascular diseases associated with hypoxia. The AT1 receptor suppression under hypoxia may be an endogenous negative feedback mechanism to prevent overactivity of RAS under tissue ischemia. Therefore, inhibition of PHD2 to support this mechanism could be a potential treatment for hypertensive end organ damage.

It should be noted that, in addition to its AT1 receptor regulation, PHD2 may regulate other genes and cellular functions through the canonical HIF1α-dependent mechanism in VSMCs. In human VSMCs, HIF1α is required for cell proliferation induced by platelet-derived growth factor, and inhibition of HIF1α attenuated neointima formation in carotid artery in response to injury. Interestingly, treatment of VSMCs with angiotensin II, thrombin, or platelet-derived growth factor induced HIF1α stabilization. Therefore, in the study by Matsuura et al,4 1% hypoxia for 24 hours caused a decrease in AT1 receptor expression. In contrast, it has been shown that 3% hypoxia increased AT1 receptor expression either directly or indirectly through suppression of inflammatory cytokines. In addition, in the study by Matsuura et al,4 1% hypoxia for 24 hours caused a decrease in AT1 receptor expression.
receptor expression and enhanced mitogenic response by angiotensin II in cultured VSMCs, which was supported by the effectiveness of the AT1 receptor blockers in decreasing hypertension associated with hypoxia in rodents and humans. Therefore, a certain mild but not severe hypoxic condition could potentially enhance the AT1 receptor function in vasculature.

In summary, the study by Matsuura et al sheds new light on vascular RAS regulation by the unique oxygen sensor PHD2. Further research in this field will potentially contribute to the development of new therapeutic approaches against cardiovascular diseases associated with enhanced RAS activity, as well as tissue hypoxia.

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**References**

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