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. HIF1α 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 2-oxoglutarate as cosubstrates and iron and ascorbate as cofactors. Cobalt (II) is known to inhibit PHDs by reducing 2-oxoglutarate as cosubstrates and iron and ascorbate as cofactors. Cobalt (II) is known to inhibit PHDs by reducing 2-oxoglutarate as cosubstrates and iron and ascorbate as cofactors. Cobalt (II) is known to inhibit PHDs by reducing 2-oxoglutarate as cosubstrates and iron and ascorbate as cofactors. CoCl₂ has been used as a PHD inhibitor as well 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 al 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 overreactivity 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 protein induction substantially more than 1% hypoxia. The induction of HIF1α by angiotensin II in VSMCs was associated with HIF1α nuclear localization and transcriptional activation through the hypoxia-responsive element. Hypoxia-independent induction of HIF1α was also observed in arteries on angiotensin II infusion and implicated in perivascular fibrosis induced by angiotensin II via expression of vascular endothelial cell growth factor.

PHD has been shown to negatively regulate nuclear factor κB (NFκB) activity by inhibition of NFκB kinase-β hydroxylation, which explains NFκB activation by hypoxia. In contrast, a PHD inhibitor, dimethyloxallyl glycine, inhibited lipopolysaccharide-induced tumor necrosis factor-α induction by reducing NFκB transcriptional activity in macrophages. Activation of NFκB has been implicated in angiotensin II–induced vascular inflammation in hypertension and diabetes mellitus. Although potential activation of HIF1α and NFκB by CoCl₂ appears negligible in the vascular fibrosis according to the findings by Matsuura et al, the therapeutic potential of vascular PHD2 inhibition remains debatable. Potential signaling interplay among angiotensin II, PHD2, HIF1α, and NFκB in mediating vascular fibrosis is illustrated in the Figure.

Multiple sis-binding elements at the AT₁ receptor promoter and their roles in regulating the AT₁ receptor expression has been well acknowledged; however, the molecular mechanism by which PHD2 inhibition can alter the AT₁ receptor promoter activity requires further clarification. PHD2 inhibition by CoCl₂ may reduce AT₁ receptor expression either directly or indirectly through suppression of inflammatory cytokines. In addition, in the study by Matsuura et al, 1% hypoxia for 24 hours caused a decrease in AT₁ receptor expression. In contrast, it has been shown that 3% hypoxia increased AT₁

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receptor expression and enhanced mitogenic response by angiotensin II in cultured VSMCs,\textsuperscript{10} which was supported by the effectiveness of the AT\textsubscript{1} receptor blockers in decreasing hypertension associated with hypoxia in rodents and humans.\textsuperscript{1,2} Therefore, a certain mild but not severe hypoxic condition could potentially enhance the AT\textsubscript{1} receptor function in vasculature.

In summary, the study by Matsuura et al\textsuperscript{4} 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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**Disclosures**

None.

**References**

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