Mechanism of Heme-Heme Oxygenase System Impairment of Endothelium Contraction in the Spontaneously Hypertensive Rat

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Heme oxygenase (HO) 1 and HO-2 gene expressions are known to increase cellular antioxidant and anti-inflammatory properties through activation of a battery of cytoprotective systems, including decreases in cyclooxygenase-1 and NADPH oxidase (NOX-2) and elevated levels of extracellular superoxide dismutase and NO. The heme-HO system (HO-1 and HO-2) acts as an endogenous anti-inflammatory and protective circuit critical for a self-resolving inflammatory-reparative process. A study by Li et al, which appears in this issue of Hypertension, shows that upregulation of heme oxygenase (HO) 1 prevents endothelium contraction in aorta of spontaneously hypertensive rats (SHRs) via a decrease in cyclooxygenase (COX) 1, not COX-2. Induction of HO-1 was observed in cultured endothelial cells and in vivo after treatment with both heme and hemoglobin. In the present article, Li et al1 showed that, in aorta isolated from either wild-type or SHR animals, levels of HO-1 are low. HO-1 under physiological conditions is expressed at low levels and does not seem to affect the basal levels of heme-dependent enzyme activity. On the other hand, HO-2, the constitutive enzyme, is the main determinant for the regulation of the basal physiological levels of various heme proteins, including COX, NOX2, inducible NO synthase, and CYP450. COX-1/2 are heme proteins that catalyze the conversion of arachidonic acid (AA) to prostaglandin H2, the precursor of prostanoids that participate in the regulation of vascular function. Heme binds to the COX apoenzyme with a stoichiometry of ≈1 heme molecule per each subunit. Accordingly, the possibility arises that variations in the cellular levels of heme impact the amount of catalytically active COX present in cells.

The cellular level of heme is regulated by the rate of its synthesis and degradation. HO-1/HO-2 control the rate-limiting step in heme degradation. Li et al1 demonstrated for the first time that induction of the heme-HO system in vascular endothelial cells participates in the regulation of prostaglandin levels in SHRs treated with heme, presumably by influencing the availability of heme required for COX-1 and COX-2, but by specifically causing a reduction in COX-1 levels. The key finding is that production of the COX-1 products, prostaglandin H2 and 6-keto prostaglandin F1α, was decreased by the heme-HO-1 system and that the nonenzymatic derivative of prostaglandin I2 was greatly diminished in SHRs treated with heme. Li et al1 report that increased HO-1 expression decreased COX-1 and not COX-2; this is different from the effect of heme on endothelial cell cultures in vitro, in which heme decreased COX-2 and not COX-1.2 These authors showed that upregulation of the heme-HO-1 system attenuated the angiotensin II–mediated increase in activity. Because heme levels are influenced by both the rate of AA acylation and reacylation, the balance determines the amount of AA available for prostaglandin release from COX activation. It is likely that alterations in COX-1 and COX-2 levels after induction of HO-1 in endothelial cells subjected to an intervention that either increased or decreased cellular heme is a consequence of a directional alteration in the levels at the COX catalytic active site.2 The Figure, shows that conditions of limited heme by HO-1 regulate vascular heme proteins. Another mechanism by which the heme-HO system impairs endothelium-dependent contraction in the aorta is via a decrease in NOX-2, another heme-dependent enzyme. A reduction in heme levels or an increase in heme turnover resulting from an increase in HO-1 expression decreased superoxide and reactive oxygen species (ROS) levels and resulted in a reduction in NADPH oxidase activity because of increased degradation of the heme-containing catalytic component of NOX-2, the gp91phox subunit.3 A similar suggestion on the role of HO-1 expression and HO activity in regulating heme-dependent enzyme-derived ROS and blood pressure elevation is described in placental ischemia–induced hypertension4 and in angiotensin II–induced renal hypertension.5 More recently, targeting the HO-1 gene to both vascular endothelial cells6 and renal tissue6 has been shown to reduce ROS and lower blood pressure. Neither of these reports assessed the effect of HO-1 induction on COX-1/COX-2 and vascular protection. It is possible that the same mechanism is functioning in a number of hypertensive models.

Based on previous work demonstrating the importance of HO-1–derived CO and bilirubin in vascular protection,7 Li et al showed that neither bilirubin nor CO derived from HO-1 prevented the impairment of endothelium contraction in the aorta of SHRs. These differences are possibly attributed to the effect of HO-1–derived CO binding to the heme moiety, thus negating the oxidant effect of heme and contributing to
the prevention of endothelial dysfunction via a decrease in CYP-derived AA metabolism to vasoconstrictors, including 20-hydroxyeicosatetraenoic acid (20-HETE).5,6 Like CO, excessive NO may also inhibit the formation of the vasoconstrictor, 20-HETE.9 We would be remiss if we did not mention the role of the heme–HO system in a reduction in vasoconstrictor (20-HETE), derived from heme–CYP450.3 In addition, the HO-1–mediated regulation of hypertension, via an increase in HO-1 expression and activity, provides vascular endothelial protection in diseases such as diabetes mellitus and mediated by upregulation of extracellular superoxide dismutase and decreases in ROS.3,10 Overall, these observations suggest that HO-1 expression has a pleiotropic effect and a major role in multiple processes that prevent endothelial dysfunction via a decrease in ROS generated by either NOX-2 or from COX activity.

In summary, the elegant work of Li et al1 demonstrates that heme–HO-1 protein expression and HO activity, not CO, influence prostaglandin production via reduction of COX-1 activation as a result of reduction in the levels of cellular heme, which decreases the 2 important heme-dependent proteins, NOX2 and COX-1. Thus, the selective pharmacological induction of the HO-1 gene targeting the vascular endothelial system represents a potential therapeutic strategy for the prevention of vascular dysfunction in hypertension. The logical extension of this work to hypertension and metabolic syndrome patients will serve to identify the novel human gene targets by which the heme–HO system lowers blood pressure and prevents the impairment of endothelium-dependent contraction and dysfunction.

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Figure. Endothelial dysfunction and the impact of the heme–heme oxygenase (HO) system on this process depend on the levels of the heme-dependent generation of reactive oxygen species (ROS) and vasoconstrictor molecules. A diagrammatic representation of the effect of the heme–HO system in blood pressure regulation is displayed. Induction of HO-1 by its substrate, heme, results in an increase of heme turnover and decreases in ROS and vasoconstrictors generated by heme-dependent enzyme systems. Decreases in the heme–HO system diminished vasoconstrictors generated by NADPH oxidase (NOX-2)-derived ROS, as well as ROS generated from activation of cyclooxygenase (COX) 1 during arachidonic acid (AA) metabolism by the aorta to prostaglandins. An additional class of vasoconstrictors not studied by Li et al1 includes AA metabolized by heme–CYP450 isoforms, which are responsible for the generation of 20-hydroxyeicosatetraenoic acid (20-HETE), a powerful vasoconstrictor. In addition, upregulation of HO-1 diminishes heme-dependent thromboxane synthesis (TXA2) and decreases mitochondrial release of ROS.

Disclosures
None.

References
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