Heme Oxygenase-1 Protects the Heart
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The seminal discovery of nitric oxide (NO) in the 1980s unraveled the novel concept that an endogenous production of a gaseous substance such as NO can impart diverse and critical functional effects on a wide spectrum of biological and pathological processes. Intense investigations in the chemistry and biology of NO have led to numerous fruitful discoveries, enhancing our understanding of many disease processes including cardiovascular disorders. Interestingly, though, we have known for a longer period of time that there exists another gaseous molecule, carbon monoxide (CO), which can be generated endogenously. The heme oxygenase (HO) enzyme system generates the majority of endogenous CO.1,2 Since the biochemical isolation of the HO enzyme in 1968, much of the focus of HO research has been in the study of HO in heme metabolism based on the known fact that the HO enzyme serves as the rate-limiting enzyme in the degradation of heme. However, in recent years, as a result of the emerging role of HO in a variety of biological processes, interest in HO has continued to grow beyond its role in heme metabolism and has expanded into many scientific disciplines. The recent characterization of the HO enzyme system in yeast, prokaryotic bacterial system, and plants further highlights the functional importance of a highly conserved enzyme throughout the evolution of living organisms.

HO catalyzes the first and rate-limiting step in the degradation of heme to yield equimolar quantities of biliverdin IXα, CO, and iron1,2 (Figure). Biliverdin is subsequently converted to bilirubin via the action of biliverdin reductase, and free iron is promptly sequestered into ferritin. Three isoforms of HO exist; HO-1 is highly inducible whereas HO-2 and HO-3 are constitutively expressed.1,2 Heme, a major substrate of HO-1, and a variety of nonheme agents including heavy metals, cytokines, hormones, endotoxin, and heat shock are also strong inducers of HO-1 expression.1,2 This diversity of HO-1 inducers has provided further support for the speculation that HO-1, in addition to its role in heme degradation, may also play a vital function in maintaining cellular homeostasis. Furthermore, HO-1 is highly induced by a variety of agents causing oxidative stress including hydrogen peroxide, glutathione depleters, UV irradiation, endotoxin, hypoxia, and hyperoxia.1,2 One interpretation of this finding is that HO-1 can serve as a key biological molecule in the adaptation and/or defense against these oxidative and cellular stresses. Indeed, many laboratories have demonstrated that induction of endogenous HO-1 provides protection against oxidative stress in various in vivo and in vitro models.1,2 Furthermore, recent analysis of HO-1−/− null mice has strengthened the evolving paradigm that HO-1 is indeed an important molecule in the host’s defense against cellular stress in that HO-1−/− null mice exhibited increased susceptibility to endotoxin.3 Interestingly, the first human case of HO-1 deficiency was recently reported.4 Analysis of this patient’s HO-1 gene revealed complete loss of exon 2 of the maternal allele and a two-nucleotide deletion within exon 3 of the paternal allele. Importantly, the human patient deficient of HO-1 expression also exhibited significant phenotypic changes reflective of homeostasis imbalance, comparable to the HO-1−/− null mice. Cells derived from this HO-1-deficient patient also demonstrated increased susceptibility to oxidative stress.5

In this issue of Circulation Research, Yet et al6 demonstrate that HO-1 provides potent cytoprotection against ischemia/reperfusion tissue injury. These investigators successfully generated cardiac-specific transgenic mice overexpressing HO-1, and by using both isolated perfused heart preparation and an in vivo myocardial infarction model, the authors provide compelling evidence that indeed HO-1 overexpression can confer marked cytoprotection against ischemia/reperfusion-induced myocardial tissue injury. This study represents an elegant extension from their previous study demonstrating that in response to chronic hypoxia, HO-1−/− null mice exhibited increased right ventricular infarcts with organized mural thrombi and increased lipid peroxidation and oxidative damage in right ventricular cardiomyocytes when compared with wild-type HO+/+ mice.6 The cytoprotective effect of HO-1 in vascular injury is further supported by a recent report by Christou et al,7 who demonstrated an important role of HO-1 in the prevention of hypoxia-induced pulmonary hypertension. By using agonists of HO-1 induction, these authors successfully showed that in vivo enhancement of HO-1 in the rat lung can prevent the development of hypoxic pulmonary hypertension and importantly inhibited the structural remodeling of the pulmonary vessel. The mechanism(s) by which HO-1 mediates these cytoprotective effects against chronic hypoxia remains to be elucidated. However, the known vasodilating and antiproliferative actions of endogenous CO, as well as indirect effect of CO, on production of vasoconstrictors and vascular growth factors such as endothelin-1 (ET-1) and platelet-derived growth factor-B (PDGF-B) may be involved in combating chronic hypoxic stress.8
The mechanism(s) by which selective overexpression of HO-1 in cardiac tissue conferred protection against ischemia/reperfusion injury remains poorly understood. The central issue of how HO-1 confers cytoprotection against cellular and tissue injury remains a major enigma in the field of HO research today and will undoubtedly continue to challenge and frustrate researchers in the foreseeable future. How does HO-1 confer such potent cytoprotection against ischemia/reperfusion tissue injury? One can speculate that the three catalytic by-products of heme catalysis by HO, namely bilirubin, ferritin from sequestration of free iron, and CO (Figure), all play critical roles in mediating cytoprotection against ischemia/reperfusion tissue injury. These speculations have been increasingly supported by experimental data (direct and indirect) in recent years. For example, the known antioxidant bilirubin has been shown to protect isolated perfused rat hearts. Although it is not known whether ferritin can directly mediate cytoprotection against ischemia/reperfusion tissue injury, ferritin is a known cytoprotective molecule in the vascular endothelium against oxidative stress. Recently, intriguing data suggest that CO may serve to protect against ischemia/reperfusion injury in the lung. The mechanism by which CO may mediate this cytoprotection perhaps is due to the potent antifibrinolytic properties of CO. Interestingly, Soares and colleagues in a recently published in vivo vascular injury model of xenotransplantation that CO not only can confer protection as effectively as HO-1 but can also confer cytoprotection in the absence of HO-1. The beneficial effects of HO-1 have also been demonstrated in ischemia/reperfusion injury in the liver. It is quite plausible that all three by-products act in concert and synergize with each other to optimize cytoprotection, depending on cell type and models of injury. The additive beneficial effect of these mediators has been shown in cultured endothelial cells, with CO and ferritin each imparting additive cytoprotection against tumor necrosis factor-α (TNF-α)-induced apoptosis. Whether it is ferritin, bilirubin, or CO, or all three of these mediators, the challenge in front of us is delineating the signaling pathways by which these molecules confer cytoprotection. The anti-inflammatory and antiapoptotic effects of HO-1 lend some clues as to how the catalytic by-products may transduce signals to provide downstream cytoprotection against cellular stresses. For example, recent observations suggest that CO may impart potent anti-inflammatory and antiapoptotic effects via the mitogen kinase pathway in macrophages and endothelial cells, respectively. Importantly, these cytoprotective effects involve neither the guanylyl cyclase–cGMP nor the NO pathway. The cGMP-independent pathway of CO perhaps reminds us that we no longer can assume that CO has to “compete” with NO for guanylyl cyclase and subsequent cGMP production for physiological function. Nevertheless, the complexity of the signaling pathways by which CO imparts cytoprotection is further highlighted by recent reports demonstrating the critical role of cGMP in mediating antifibrinolytic and antiproliferative effect of CO in ischemia/reperfusion and vascular injury models.

As observed in many physiological, biological, and toxicological systems, overzealous production of effector molecules may be counterproductive for the maintenance of cellular and organismal homeostasis during both normal and pathophysiological conditions. Hence, the levels of cytoprotective genes are usually induced by cellular stresses, rather than constitutively expressed. In the case of the HO enzyme system, ironically, at one time or another in the past (still is), each of three catalytic by-products of heme degradation by HO has been a known cellular toxin. For example, the released iron from breakdown of heme can serve as a potent oxidant molecule facilitating the production of hydroxyl radicals via the Fenton reaction. Bilirubin plays an important role in the development of kernicterus. The lethality of CO is well known by its ability to bind to the oxygen-carrying heme moiety of hemoglobin, dissociating oxygen and depriving tissues of their oxygen supply; CO remains the most common cause of poison-related deaths in the United States. Thus, the HO enzyme system, which possesses both constitutive and inducible isoforms, is poised and ready to “switch” the signal, when stressed, with an appropriate level of HO-1 induction to combat cellular stresses. Once induced, the HO-1 molecule is uniquely qualified to thwart deleterious toxins by the liberation of bilirubin, ferritin, or CO for cellular protection.

Ample evidence now exists that HO-1 plays a critical role in the adaptive response of cells and tissues to a variety of stresses. There is hard work in front of us: we need to delineate more precisely the mediators of cytoprotection of HO-1 and the biochemical and cellular mechanism(s) by which HO-1 or its catalytic by-products confer cytoprotection.

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References


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