Atherosclerosis
Defeat of the Defense?
Ton J. Rabelink, Erik Stroes

Heme oxygenases (HOs) are rate-limiting enzymes that catalyze the conversion of heme into equimolar amounts of biliverdin, carbon monoxide (CO), and iron. Biliverdin is subsequently reduced to bilirubin pigment by biliverdin reductase. The heme oxygenases consist of 2 major isoforms, HO-1 and HO-2. Whereas HO-2 is constitutively produced within the brain, testes, and the endothelium, HO-1 gene expression is inducible by heme, cytokines, nitric oxide (NO) donors, and agents and conditions associated with increased oxidant stress, eg, oxidized LDL and ischemia/reperfusion injury. HO-1 induction has been shown to have potent antioxidant effects. Indeed, HO-1 knockout mice are more sensitive toward oxidant insults, whereas HO-1 is upregulated in models associated with increased oxidative stress, such as sepsis, organ transplantation, and atherosclerosis. Increased sensitivity to oxidant injury was also one of the hallmarks of a recently described patient with HO-1 deficiency. The potential importance of HO-1 as an antioxidant system in humans is underscored by the observation that a microsatellite polymorphism in the promoter region of the HO-1 gene could be linked to the decreased inducibility of HO-1 and associated with the development of emphysema in smokers.

The antioxidant effect of HO-1 can be explained by several mechanisms. First, HO-1 degrades the intracellular pro-oxidant heme. In addition, the resulting product, bilirubin, can act as a potent peroxy radical scavenger. In this respect, the reduction of leukocyte adhesion during oxidative stress by HO-1 induction could largely be attributed to the antioxidant effects of bilirubin. HO-1 also results in the generation of CO, which has antiatherogenic and vasodilating properties mediated via cGMP. CO also has the ability to inhibit cytochrome P-450, which can promote oxidation of fatty acids. In this respect, HO-1 could serve as a backup mechanism for the impaired NO availability during atherogenesis, when increased HO-1 expression can result in the production of bilirubin and CO. In this scenario, bilirubin and CO act as a cellular antioxidant and a vasodilator, respectively.

In this issue of Circulation Research, Ishikawa et al. describe how pharmacological modulation of HO-1 can alter atherogenesis in LDL receptor knockout mice. Induction of HO-1 with hemin (z-deferoxamin) resulted in smaller atherosclerotic lesions, whereas inhibition of HO-1 with Zn-protoporphyrin IX resulted in larger lesions compared with controls. This study corroborates the importance of vascular defense mechanisms against oxidant stress in the course of atherogenesis. Indeed, many key events during atherogenesis have been related to increased oxygen radical stress, including oxidative modification of lipids, induction of proinflammatory genes, increased cellular proliferation, and alterations of NO availability. HO-1 induction is a natural response to increased oxidative stress. However, recent data from the same group of investigators show that strong upregulation of HO-1 is not sufficient to protect the vessel wall from development of atherosclerosis. Therefore, the question arises as to how specific additional activation of HO-1 could be achieved in the clinical setting. Pharmacological induction of heme oxygenases in the clinical setting is very complex. Hemin, for example, may also induce lipid peroxidation and could play a detrimental role in the potential link between increased iron status and cardiovascular disease. Alternative procedures to obtain HO-1 induction, such as exposure to endotoxin and cytokines, certainly have their limitations. Interestingly, NO donors have recently been shown to cause HO-1 induction, most likely attributable to the activation of soluble guanylate cyclase. However, NO donors such as 3-morpholinosydnonimine (SIN-1) and S-nitroso-N-acetylpenicillamine (SNAP) are characterized by simultaneous release of both reactive nitrogen and oxygen species. Therefore, comparable to the setting of atherosclerosis, HO-1 induction by these drugs may to some extent also reflect a response to redox activation. Nevertheless, modulation of vascular cGMP, either by NO donors, by cGMP itself, or by the natriuretic peptides, presently seems to be the most promising tool to pharmacologically modulate HO-1 induction. HO-1 could also be considered a target for local vascular gene therapy. In obese Zucker rats, HO-1 transduction has been shown to attenuate ischemia/reperfusion injury and to prolong survival after liver transplantation. It is certain, however, that additional studies are needed to extrapolate this finding to (local) atherogenesis and neointimal hyperplasia.

Unfortunately, the present study by Ishikawa et al does not offer insight into the mechanisms responsible for HO-1–related effects. Both the reduction in lipid peroxidation and the increase in NO bioavailability could be the result of an antioxidant effect. However, the mechanism responsible for this antioxidant effect was not addressed in the study by Ishikawa et al. Additional elucidation of this mechanism...
may provide the key to a deeper understanding of the failure of this defense system during atherogenesis (despite its upregulation).22 One interesting hypothesis is that NO requires adequate antioxidant mechanisms to be able to exert its actions. Indeed, the reaction coefficient of NO and superoxide exceeds that of the enzymatic antioxidant systems, making NO availability dependent on the level of oxyradical stress. In this respect, it makes sense that NO induces enzymatic antioxidant systems, such as HO-1 and extracellular superoxide dismutase (SOD).26 As a consequence, it can be argued that the efficacy of the antioxidant defense systems in countering atherosclerosis is critically dependent on the prevailing NO status.

In conclusion, the HO system has come a long way, from an enzyme predominantly responsible for heme degradation to a potential defense mechanism against the development of atherosclerosis. Although most of our clinical efforts in the treatment of atherosclerosis presently focus on reducing risk factors, ie, reducing the insults to the vascular wall, the study by Ishikawa et al20 reemphasizes the potential of targeting the HO system during atherogenesis (despite its upregulation).22 One interesting hypothesis is that NO reuptake provides the key to a deeper understanding of the failure of this defense system during atherogenesis (despite its upregulation).22 One interesting hypothesis is that NO requires adequate antioxidant mechanisms to be able to exert its actions. Indeed, the reaction coefficient of NO and superoxide exceeds that of the enzymatic antioxidant systems, making NO availability dependent on the level of oxyradical stress. In this respect, it makes sense that NO induces enzymatic antioxidant systems, such as HO-1 and extracellular superoxide dismutase (SOD).26 As a consequence, it can be argued that the efficacy of the antioxidant defense systems in countering atherosclerosis is critically dependent on the prevailing NO status.

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References


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