Editorial Commentary

Heme Oxygenase-1 Inhibition of Nox Oxidase Activation Is a Microvascular Endothelial Antioxidant Effect of NO

Michael S. Wolin, Nader G. Abraham

A study by Jiang et al1 in this issue of Hypertension reports evidence suggesting that NO has a novel antioxidant-type effect in cultured human microvascular endothelial cells associated with an inhibition of Nox oxidase activation, which seems to be mediated by increasing the expression and activity of heme oxygenase-1 (HO-1). The induction of HO-1 was observed to occur when the cultured endothelium was exposed to a long-acting NO donor for ≥6 hours. Because freshly isolated vascular tissue from normal animals is generally thought to contain low levels of HO-1, the levels of NO seen in endothelium under physiological conditions do not seem to be a stimulus for maintaining an elevated level of this enzyme.

Physiological stresses associated with oxidant production were initially observed to increase HO-1 expression in multiple tissue preparations.2 The formation of reactive NO-derived species (NOX) from the reaction of NO with superoxide, such as peroxynitrite, were initially observed to promote HO-1 expression in endothelial cells exposed to NO donors in a manner that was modulated by free thiol availability.3 Although the precise mechanism involved in how NOX induces HO-1 expression is currently not known, the gene for HO-1 has many sites in its promoter region for redox regulation by intracellular and nuclear signaling events that lead to transcriptional activation.2 Thus, increases in HO-1 expression by elevated levels of NO are likely to occur when endothelium is exposed to physiological stress or pathophysiological conditions associated with vascular disease processes, such as hypertension.

The decreased detection of superoxide associated with induction of HO-1 by NO in endothelium was investigated to assess whether it was related to alterations in the expression of Nox oxidase subunits or Cu,Zn-superoxide dismutase (SOD) or a pattern of effects that could be equated with the increased activity of HO-1.1 Inhibition of HO activity or prevention of increased HO-1 expression with small interfering RNA attenuated the effects of exposure to NO, suggesting that the catalytic activity of HO-1 and not an alternative effect of NO on superoxide scavenging is responsible for the antioxidant effects of NO that were detected. The heme-depleting activity resulting from increased HO-1 expression was observed in a previous study4 to decrease NADPH oxidase activity in macrophages through processes thought to involve impairment of protein maturation and increased degradation in its heme-containing catalytic component, the gp91phox (Nox2) subunit. However, in the present study it was observed that cellular levels of the key heme-containing Nox subunits present in endothelium, other subunits thought to regulate the Nox oxidases investigated, and Cu,Zn-SOD were not altered by the increased HO-1 expression elicited by exposure to NO.1 These data on the absence of detectible changes in Nox oxidase expression also rule out another recently reported mechanism5 involving NO donors inhibiting the expression of mRNA for Nox1. Thus, the superoxide-depressing effects of exposure of endothelium to NO seemed to be associated with an increased HO-1 activity and not with an alternative antioxidant action of NO or a change in the expression of Cu,Zn-SOD or key components of Nox oxidases present in endothelium.

The product of the metabolism of heme by the HO-1 reaction, bilirubin, was observed to have an action potentially associated with decreasing Nox oxidase activation by a p47phox-dependent mechanism,1 which could contribute to the antioxidant effects of increased HO-1 expression by NO. An early observation made in studies characterizing modulation of the activation of Nox oxidase in neutrophils was that bilirubin, a key metabolic product of increased heme metabolism by HO, interacted with a cytosolic component in a manner that inhibited the activation of superoxide production by this oxidase.6 Bilirubin has also been observed to inhibit what seems to be a growth factor activation of Nox oxidases in airway smooth muscle cells.7 Although the mechanism through which bilirubin inhibits Nox oxidase activation is not known, data in the study of Jiang et al1 suggest that this agent may interfere with the membrane binding of p47phox associated with Nox oxidase activation or possibly the protein kinase C–p47phox is likely to activate Nox oxidases and superoxide production by this oxidase.6 Bilirubin has also been observed to inhibit what seems to be a growth factor activation of Nox oxidases in airway smooth muscle cells.7 Although the mechanism through which bilirubin inhibits Nox oxidase activation is not known, data in the study of Jiang et al1 suggest that this agent may interfere with the membrane binding of p47phox associated with Nox oxidase activation or possibly the protein kinase C–p47phox is likely to activate Nox oxidases and superoxide production by this oxidase.6

Overall, the results of the study of Jiang et al1 support a mechanism shown in the Figure according to which prolonged exposure to NO elicits increased expression of HO-1, and the generation of bilirubin, resulting from the metabolism of heme by this enzyme, attenuates Nox oxidase–derived superoxide production by preventing oxidase activation by p47phox-dependent pathways. Based on previous work in the literature demonstrating the potential importance of NO, in increasing the expression of HO-1 and the redox stress-associated regulation of transcriptional activation of this gene,2,3 NO, derived from the reaction of superoxide with NO or the oxidation of NO are likely to mediate the increased HO-1 expression caused by prolonged exposure of endothelium to NO.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000242338.42238.d6

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Known effects of the HO-1 reaction, including removing the oxidant effects of heme, and additional oxidant scavenging and signaling actions of bilirubin and carbon monoxide probably also contribute to preventing endothelial dysfunction when NO is forming as a result of exposure to NO. Thus, endothelial HO-1 induction by NO may function as a feedback protective mechanism to preserve NO-mediated endothelial regulation of vascular function. It has been observed that increasing the expression of HO-1 in vivo has protective effects on NO regulation of vascular function in diseases such as diabetes associated with an upregulation of other important antioxidant systems protecting the vasculature, such as extracellular SOD and plasma catalase activity. Overall, these observations suggest that increased HO-1 expression may have a major role in multiple processes that prevent endothelial dysfunction and preserve vascular regulation by NO derived from endothelial NO synthase activity, which are generally associated with systems controlled by stimulation of soluble guanylate cyclase activity. Thus, antioxidant effects of NO-elicited increases in HO-1 expression could participate in preventing endothelial dysfunction seen in vascular diseases, which are often associated with a loss of NO-mediated vasodilation, enhanced vascular smooth proliferative remodeling, thrombosis, and inflammatory cell activation.

Sources of Funding

Our laboratories are funded by National Institutes of Health grants HL31069, HL43023, and HL66331 (M.S.W.) and HL34300 and HL55601 (N.G.A.).

Disclosures

None.

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Hypertension. 2006;48:826-827; originally published online September 18, 2006; doi: 10.1161/01.HYP.0000242338.42238.d6
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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