

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



*Learn and Live*SM

Gene Targeting and Heme Oxygenase-1 Expression in Prevention of Hypertension Induced by Angiotensin II

Nader G. Abraham

Hypertension 2008;52;618-620; originally published online Aug 11, 2008;

DOI: 10.1161/HYPERTENSIONAHA.108.117762

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2008 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/cgi/content/full/52/4/618>

Subscriptions: Information about subscribing to Hypertension is online at
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Gene Targeting and Heme Oxygenase-1 Expression in Prevention of Hypertension Induced by Angiotensin II

Nader G. Abraham

The report by Vera et al¹ that appears in this issue demonstrates that the kidney-specific induction of heme oxygenase (HO)-1 prevents angiotensin (Ang) II hypertension in CL57BL/6J mice. Kidney-specific induction of HO-1 was achieved by implanting intrarenal medullary interstitial catheters in the left kidney of uninephrectomized mice. Infusion of cobalt protoporphyrin, a known inducer of HO-1, produced a significant induction of HO-1 protein levels and increased HO activity largely in the renal medulla. Ang II–dependent hypertension was examined by measuring mean arterial pressure and was found to be attenuated in cobalt protoporphyrin–treated animals. The levels of heme, the substrate of HO, and superoxide were increased in Ang II–treated animal. These increases were blocked in cobalt protoporphyrin–treated animals. The authors conclude that the specific induction of renal HO-1 is responsible for the prevention of Ang II–dependent hypertension and the lowering of blood pressure in this animal model of hypertension.

This article raises important findings related to gene targeting in renal injury and HO-1. As shown previously, the degradation of heme is regarded as pivotal in cellular defense for 2 reasons. First, the pro-oxidant heme is removed and, second, increased production of bilirubin/biliverdin and CO, heme degradation products, is now considered beneficial to cellular cytoprotection. Iron, the third heme degradation product, which can stimulate free radical formation, is immediately bound by ferritin. Thus, CO and bilirubin are central to the defense mechanisms that occur in times of stress, a result of elevated levels of HO-1 protein and HO activity. The HO-1/HO-2 system has been long implicated in the regulation of renal function and hypertension (reviewed in Reference 2). Sacerdoti et al³ first reported the benefits of an acute effect, describing that treatment with stannous chloride prevented the development of high blood pressure in the spontaneously hypertensive rats. Subsequently, others reported that acute and chronic expression of HO-1 decreased vasoconstrictors, such as 20-HETE,⁴ thromboxane synthase activity, and cyclooxygenase (COX)-2 activity.

Heme arginate, or heme, which is used clinically for the treatment of porphyria,⁵ has been shown to have a beneficial effect on acute induction of HO-1 and to lower blood pressure in hypertensive rats.⁶

Ang II is systematically and/or locally elevated in many forms of hypertension and is associated with increased vascular O₂⁻ production. Increased O₂⁻ has been shown to contribute to the vascular and renal effects of Ang II.⁷ Previous studies have documented the induction of vascular, cardiac, and renal HO-1 in response to Ang II in vitro and in vivo.² HO-1 protein was shown to be markedly increased in aortic adventitial and endothelial cells from rats with Ang II–induced hypertension; however, treatment with losartan, a selective Ang II type 1 receptor antagonist, blocked the upregulation of HO-1. An increase in HO-1 gene levels may interrupt the vasoconstrictor pathway and attenuate the inflammatory aspect of the microcirculation in hypertension, ie, oxidative stress, leukocytes/endothelial interaction, and apoptosis, by increasing bilirubin and CO, which are of overriding importance in the pathogenesis of vascular injury. Thus, the ability to upregulate the HO-1 pathway offers a unique therapeutic approach to the control of hypertension.

In renovascular hypertension, the products of the arachidonic acid metabolic pathway, mediated by the hemoproteins COX and cytochrome P450, have been reported, in animal models, to contribute to hypertension.² HO has been implicated as a major regulator of several cytochrome P450s, including those responsible for the formation of 20-HETE, of which the production has been linked to increased blood pressure.^{8–10} As seen in the Figure, an excess of reactive oxygen species (ROS) can occur, because of an increase in Ang II levels, an increase of proinflammatory molecules, or a decreased rate of removal of ROS by extracellular superoxide dismutase and other scavengers. ROS generated will convert NO to ONOO⁻, a toxic substance that causes denaturation of heme proteins and contributes to renal cell death. ROS increase HO-1 protein levels, whereas ROS inhibit HO activity. Therefore, targeting HO-1 to a renal specific site, such as proximal tubules or renal vessels, will result in degradation of both denatured heme protein and free heme. Induction of HO-1 will decrease the inducible heme-dependent enzymes, such as inducible NO synthase, reduced nicotinamide-adenine dinucleotide phosphate oxidase, and cytochrome P450 ω/ω -1 hydroxylase. Expression of ω/ω -1 hydroxylase has differential effects in the thick ascending loop of Henle that result in vasodilation but in renal interlobar arteries lead to vasoconstriction. Ang II increases levels of 20-HETE, and 20-HETE exacerbates the Ang II–mediated

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

From the Department of Pharmacology and Medicine, New York Medical College, Valhalla.

Correspondence to Nader G. Abraham, Department of Pharmacology and Medicine, New York Medical College, Basic Science Building, Valhalla, NY 10595. E-mail nader_abraham@nymc.edu

(*Hypertension*. 2008;52:618-620.)

© 2008 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.108.117762

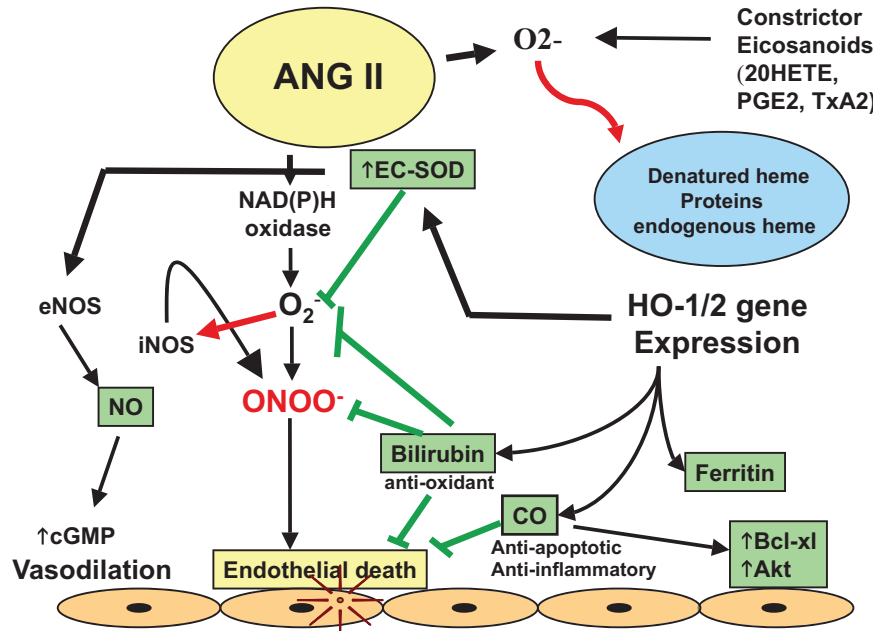


Figure. Diagrammatic representation of the effect of Ang II and arachidonic acid in the control of blood pressure in relation to HO-1. The increase of HO-1 increases Ferritin synthesis and anti-inflammatory properties, as a result of sequestering iron. CO and bilirubin will increase pAKT and BCL-2, which are antiapoptotic signaling molecules. CO also has antiinflammatory properties. Bilirubin and CO prevent endothelial damage and sloughing in conditions such as hypertension via an increase in extracellular superoxide dismutase and attenuate oxidation of low-density protein in renal interlobar arteries and various renal vessels. Increase of HO-1 in the vascular system will attenuate the generation of various constrictor molecules, such as prostaglandin (PG) E₂ (COX-2), 20-HETE, and CYP450. HO-1 induction decreases the levels of inducible proteins, including inducible NO synthase (iNOS), COX-2, and CYP4A type (prohypertensive), but not the epoxygenase pathway and the generation of epoxyeicosatrienoic acids (EETs), (antihypertensive) and subsequently decreases the vasoconstriction effect of Ang II. Finally, at the vascular level, HO-1 targeting to the endothelium may prevent endothelial cell death and restore vascular integrity.²

increase in ROS. This cycle can be prevented by selective overexpression of HO-1 (Figure). It is clear that the presence and inducibility of HO-1 in the kidney, together with the known action of its catalytic products, CO and bilirubin, suggest a critical role for HO-1 in the regulation of urine volume, electrolyte excretion, and blood pressure.² Therefore, site-specific expression of HO-1 that attenuates Ang II-mediated renal dysfunction as reported by Vera et al¹ opens a new avenue of investigation.

A study using clipped and nonclipped kidneys from 2-kidney, 1-clip hypertensive rats reported induction of HO-1 and increased HO activity, as well as increased levels of the antiapoptotic molecules Bcl-2 and Bcl-xL and decreased levels of the apoptotic molecules caspase 3 and caspase 9. The induction of HO-1 has been shown to lower blood pressure and superoxide production of Ang in hypertensive mice.² Overexpression of HO-1 significantly attenuated the pressor responsiveness to Ang II in rats transduced with retroviruses containing the human HO-1 gene. The induction of HO-1 also attenuates the development of hypertension and renal injury, leading to a decrease in Ang II-induced injury and salt-sensitive hypertension.² This study further emphasized the antiapoptotic action of the HO system as an important protective mechanism in kidney pathology and suggested that this pathway could be a specific target in the treatment of hypertension.

Direct evidence for the role of CO in vascular response was presented when it was shown that a reduction in CO generation resulted in increased vascular resistance in rat liver.

Subsequent studies have shown clearly that HO-1-derived CO and bilirubin result in a vasorelaxant effect not only via cGMP-dependent but also via cGMP-independent² stimulation of certain K channels and an increase in adiponectin levels. The biological actions of bilirubin may be especially relevant to the prevention of oxidant-mediated cell death.² Bilirubin, at a low concentration, scavenges ROS in vitro, thereby reducing oxidant-mediated cellular damage and attenuating oxidant stress in vivo.

In summary, the report by Vera et al¹ focuses on the role of renal HO-1 in preventing Ang II hypertension. There are, however, several possible mechanisms for the antihypertensive effects, including the antioxidant role of bilirubin, antiapoptotic role of CO, pro-oxidant role of heme, and regulatory actions of various metabolites of the arachidonic acid cascade. It is important to remember that increased HO activity results in a reciprocal decrease in inducible heme-dependent proteins, such as COX-2, inducible NO synthase, TxA₂ synthase, and CYP450-mediated 20-HETE, that are intimately involved in the regulation of renal function and hypertension. This report is important because it highlights the central role of HO-1 induction in preventing hypertension and in clinical intervention. Additional investigations that attempt to elucidate the mechanism by which the HO-1 gene targeting the renal structure in a renal site-specific manner delays or prevents hypertension would help to clarify this issue. Additional research in hypertensive patients will serve to identify the mechanism by which heme arginate lowers blood pressure in this patient popu-

lation.⁵ Evaluation of gain-of-function and loss-of-function for HO-1 in renal tissue using transgenic models could also be of crucial value to understanding the results of Vera et al.¹

Sources of Funding

This work was supported by National Institutes of Health grants DK068134, HL55601, and HL34300.

Disclosures

None.

References

1. Vera T, Kelsen S, Stec DE. Kidney-specific induction of heme oxygenase-1 prevents angiotensin II hypertension. *Hypertension*. 2008;52:660–665.
2. Abraham NG, Kappas A. Pharmacological and clinical aspects of heme oxygenase. *Pharmacol Rev*. 2008;60:79–127.
3. Sacerdoti D, Escalante B, Abraham NG, McGiff JC, Levere RD, Schwartzman ML. Treatment with tin prevents the development of hypertension in spontaneously hypertensive rats. *Science*. 1989;243:388–390.
4. da Silva JL, Tiefenthaler M, Park E, Escalante B, Schwartzman ML, Levere RD, Abraham NG. Tin-mediated heme oxygenase gene activation and cytochrome P450 arachidonate hydroxylase inhibition in spontaneously hypertensive rats. *Am J Med Sci*. 1994;307:173–181.
5. Kordac V, Kozakova M, Martasek P. Changes of myocardial functions in acute hepatic porphyrias. Role of heme arginate administration. *Ann Med*. 1989;21:273–276.
6. Levere RD, Martasek P, Escalante B, Schwartzman ML, Abraham NG. Effect of heme arginate administration on blood pressure in spontaneously hypertensive rats. *J Clin Invest*. 1990;86:213–219.
7. Ortiz PA, Garvin JL. Superoxide stimulates NaCl absorption by the thick ascending limb. *Am J Physiol Renal Physiol*. 2002;283:F957–F962.
8. Singh H, Cheng J, Deng H, Kemp R, Ishizuka T, Nasjletti A, Schwartzman ML. Vascular cytochrome P450 4A expression and 20-hydroxyecosatetraenoic acid synthesis contribute to endothelial dysfunction in androgen-induced hypertension. *Hypertension*. 2007;50:123–129.
9. Fleming I. Cytochrome P-450 under pressure: more evidence for a link between 20-hydroxyecosatetraenoic acid and hypertension. *Circulation*. 2005;111:5–7.
10. Alonso-Galicia M, Maier KG, Greene AS, Cowley AW Jr, Roman RJ. Role of 20-hydroxyecosatetraenoic acid in the renal and vasoconstrictor actions of angiotensin II. *Am J Physiol Regul Integr Comp Physiol*. 2002;283:R60–R68.