Editorial Commentary

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

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The report by Vera et al\(^1\) 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 al\(^3\) 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 \(O_2^-\) production. Increased \(O_2^-\) 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.\(^8\) 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.\(^8\) 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 \(w/o\)-1 hydroxylase. Expression of \(w/o\)-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

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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. Therefore, site-specific expression of HO-1 that attenuates Ang II–mediated renal dysfunction as reported by Vera et al 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. Overexpression of HO-1 that attenuates Ang II–mediated renal dysfunction as reported by Vera et al opens a new avenue of investigation.

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-independent 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. 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 al 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-
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

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References

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