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Heme oxygenase: the key to renal function regulation

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Abraham NG, Cao J, Sacerdoti D, Li X, Drummond G. Heme oxygenase: the key to renal function regulation. *Am J Physiol Renal Physiol* 297: F1137–F1152, 2009. First published July 1, 2009; doi:10.1152/ajprenal.90449.2008.—Heme oxygenase (HO) plays a critical role in attenuating the production of reactive oxygen species through its ability to degrade heme in an enzymatic process that leads to the production of equimolar amounts of carbon monoxide and biliverdin/bilirubin and the release of free iron. The present review examines the beneficial role of HO-1 (inducible form of HO) that is achieved by increased expression of this enzyme in renal tissue. The influence of the HO system on renal physiology, obesity, vascular dysfunction, and blood pressure regulation is reviewed, and the clinical potential of increased levels of HO-1 protein, HO activity, and HO-derived end products of heme degradation is discussed relative to renal disease. The use of pharmacological and genetic approaches to investigate the role of the HO system in the kidney is key to the development of therapeutic approaches to prevent the adverse effects that accrue due to an impairment in renal function.

stress response genes; antioxidants; transcriptional factors; antiapoptosis; inflammation; acute kidney injury; diabetic nephropathy; hypertension; obesity; carbon monoxide; bilirubin

HEME IS THE PROSTHETIC GROUP of a number of enzymes and thereby influences endothelial cell (EC) function through the regulation of the activities of numerous proteins, including nitric oxide synthase (NOS), P-450, cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and catalase (7). Heme oxygenase (HO) lowers cellular levels of heme by catalyzing the stereospecific opening of the heme ring resulting in the production of biliverdin, the release of iron, and the attendant emission of carbon monoxide (CO; Ref. 127). Excess heme causes vascular dysfunction (1).

Clinical studies (129) have shown that heme administration can precipitate acute tubular necrosis and that the HO system reduced tissue injury in the kidney. HO primarily exists in two isoforms, the products of different genes. HO-1 is induced by numerous compounds in stressed organs and tissues; HO-2, the constitutive isozyme, has as its only major stimulus, corticosteroids (37). HO-1 is induced by oxidant stress, and a robust increase in HO-1 expression provides protection against oxidative insults (68, 203, 205) and has led to an examination of the antioxidant nature of HO-1 and HO-2 (6, 10, 18). HO-1 degrades excess heme supplied by either mitochondria or destabilized heme proteins (130). Heme degradation products, carbon monoxide (CO), biliverdin/bilirubin, and iron/ferritin, possess potent antioxidant properties (75) and antiapoptotic effects (8, 165; Fig. 1). Subsequent studies (20) indicate HO-1 exerts its cytoprotective properties not only by removing the prooxidant heme and producing bilirubin, a potent antioxidant,

but also by maintaining iron homeostasis through the synthesis of ferritin thereby preventing iron from serving as a catalyst for oxidant stress. A substantial and rapidly growing literature indicates that the HO-1/HO-2 system is a regulator of both renal vascular integrity and oxidative stress.

This review focuses on the involvement of the HO system in prevention of renal injury and vascular disease including obesity. The cytoprotective properties of the products derived from HO system are also discussed in this review.

HO Isoform Expression in Kidney

Studies have implicated specific sites of the HO isoforms in the kidney important for the preservation of renal vascular and tubular function. Normally, HO-1 protein is weakly expressed in the cortex and in the outer medulla of kidney. HO-1 protein levels increased after reperfusion and returned to basal concentration by 12 h (192). HO-2 has been shown to be constitutively expressed primarily in arteriolar homogenates and to a lesser extent in the thick ascending limb and proximal tubules (39). The occurrence of both isozyme mRNAs was highest in the renal inner medulla and lowest in the renal cortex (230).

HO participates in the regulation of renal circulation and sodium excretion (108). Inhibition of HO activity in the renal interstitium preferentially reduces medullary blood flow (230), while augmentation of HO-1 can attenuate the release of vasoconstrictors and reduce blood pressure in spontaneously hypertensive rats (SHR; Ref. 55). The blood pressure lowering effect of HO-1 can be attributed to various mechanisms, including decreased production of vasoconstrictor eicosanoids and increased production of CO, which functions as a vasodilator, a stimulator of soluble guanylate cyclase, an endogenous

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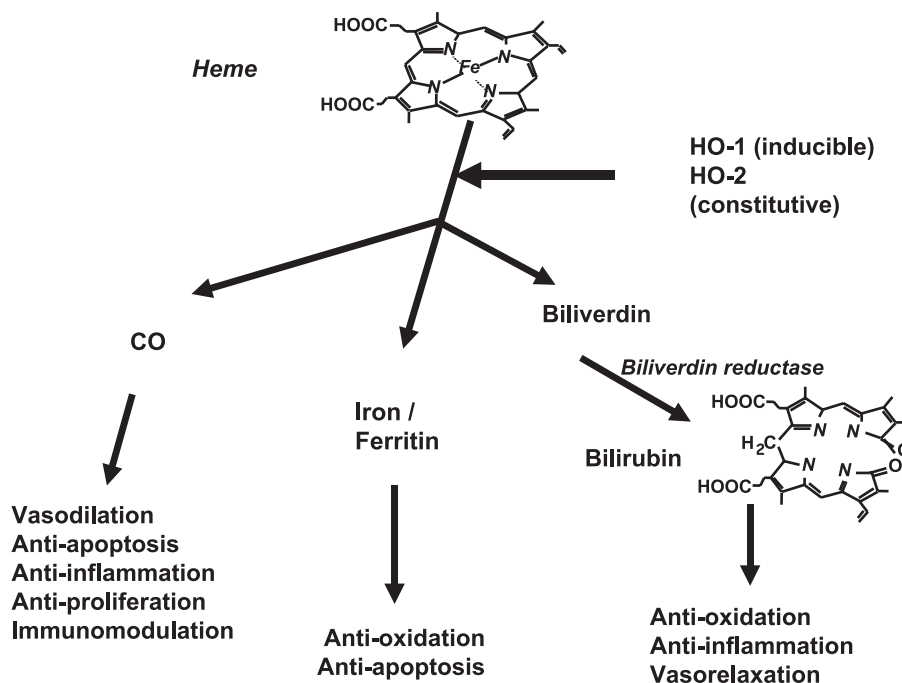


Fig. 1. Heme oxygenase (HO), the rate limiting enzyme in heme degradation exists in two isoforms, HO-1 (inducible) and HO-2 (constitutive). Functional consequences of the three heme degradation products, biliverdin, iron, and carbon monoxide (CO). Biliverdin is converted to bilirubin in a stereospecific manner by the cytosolic enzyme biliverdin reductase. Both CO and bilirubin are bioactive molecules, while the iron generated by heme degradation is immediately sequestered by associated increases in ferritin.

modulator of the cGMP signaling system, an activator of calcium-activated potassium channels in vascular smooth muscle, and an inhibitor of endothelin-1 (60, 227). Acute elevation of renal perfusion pressure (RPP) induced a rise of CO and nitric oxide (NO) concentrations accompanied in the medullary tissue by natriuresis (108). Chromium mesoporphyrin inhibits HO activity in the medulla and, when infused into the renal interstitium, reduces both basal- and RPP-stimulated CO and NO levels, salt, and water excretion. Moreover, inhibition of HO activity blunts the diuresis and natriuresis associated with an acute increase in RPP. The blockade of the renin-angiotensin-aldosterone system by HO-1 upregulation interrupts the increase of blood pressure in renovascular hypertension (23). Thus basal HO activity, at least partially, participates in the maintenance of renal blood flow, vasotonic balancing, and sodium and fluid absorption in the loop of enle.

Tin chloride, a potent and specific inducer of renal HO-1, ameliorated the ischemic renal injury as judged by the significant decrease in serum creatinine and blood urea nitrogen levels and a decrease in blood pressure (169; reviewed in Ref. 1) reduction in tubular epithelial cell injury (192). Interestingly, the pharmacological induction of HO-1 led to a significant decrease in microsomal heme content, which may represent a further cytoprotective mechanism; in fact, heme functions as a prosthetic group of a number of key enzymes in the pathophysiological processes of renal injury such as NOS, COX, and NADPH oxidase. Similarly, pharmacological or retroviral-mediated induction of HO-1 led to heme depletion and consequently to decreased COX activity (103). Furthermore, a decrease in heme content due to HO-1 activation limited heme availability for inducible heme proteins including inducible NOS (iNOS) and the maturation of the gp91(phox) subunit and assembly of the functional NADP(H) oxidase and thus attenuated free radicals formation and oxidative stress damage (186). Quan et al. (155), employing an adenoviral vector expressing human HO-1 under the control of the thick ascending

limb of Henle (TALH)-specific promoter $\text{Na}^+ - \text{K}^+ - \text{Cl}^-$ cotransporter, demonstrated a site-specific expression of HO-1 and a TALH-selective protection vs. oxidative stress in the kidney.

CO and Renal Function

The majority of CO produced *in vivo* results from the degradation of heme by HO (reviewed in Refs. 1; 182, 207). The antihypertensive effect of CO stems from the observation that upregulation of the HO/CO system lowered blood pressure in young but not in adult SHR (169). Subsequently, it was reported that CO and NO had similar properties (124), in that both molecules behaved as messenger and signaling molecules. CO and NO are capable of inducing the relaxation of blood vessels through vasodilation and of inhibiting the proliferation of vascular smooth muscle cells (181). CO was reported to influence the soluble guanine cytosine and cGMP pathways that serve to regulate both blood pressure and vascular contractility (132). Interestingly, CO-regulated blood pressure works together with NO in hypertensive rats by impairing both the function and production of NO (197). Direct evidence for the role of CO in vascular response was demonstrated by a reduction in CO generation, which resulted in increased vascular resistance in the rat liver (184). Subsequent studies have shown that HO-1-derived CO and bilirubin produce a vasorelaxant effect not only via cGMP-dependent but also via cGMP-independent (106, 138) stimulation of certain K channels (48, 208–210). CO-mediated relaxation is not dependent on the cGMP pathway but is dependent on the activation of bradykinin large-conductance Ca^{2+} channels (BK_{Ca} ; reviewed in Ref. 1), and is abolished by blockers of BK_{Ca} channels (101). Therefore, the vasodilatory effect of CO may be dependent on the level of NO, BK_{Ca} activities, and soluble guanylate cyclase, among other factors. CO inhibits NO-mediated relaxation in conditions of elevated NO levels. HO-1-derived CO also increases adiponectin levels (reviewed in Refs. 1, 95). Adiponec-

tin has beneficial effects on vascular function (213). Furthermore, it is unlikely that CO and NO represent redundant messenger molecules, even though both are active in the vessel wall. Recent studies (190) have shown that HO-derived CO may either regulate or inhibit NOS and contribute to hypertension and endothelial dysfunction in Dahl salt-sensitive rats. A CO-releasing molecule, Ru (CO) 3 Cl (glycinate) (CORM-3), rendered ECs resistant to oxidative stressors (157). CO produced from heme metabolism in blood vessels was reported to elicit relaxation (78, 208) through the elevation of cGMP levels (123). Hemin, an inducer of HO, was reported to decrease blood pressure in the pulmonary artery of young SHR (133). CO can induce vasorelaxation by stimulating cGMP and calcium-activated potassium channels (8; Fig. 2).

Recent studies demonstrate that CO inhalation therapy protects renal grafts from ischemic damage in experimental models. In a rat model of transplant-induced I/R injury, inhalation of 250 ppm of CO gas resulted in a significant improvement of graft renal function as measured by glomerular filtration rate and creatinine levels (134). Ultrastructural improvement was observed following CO inhalation manifested by viable podocytes, preservation of foot processes, less frequent vacuolization, and maintenance of internal cellular architecture. Furthermore, CO inhalation resulted in a significant reduction of tubular epithelial cell apoptosis and, similar to biliverdin administration, showed a significant decrease in IL-6, IL-1, intercellular adhesion molecular (ICAM)-1, iNOS, and nitrite/nitrate formation.

CORM-3 when administered before the onset of ischemia significantly decreased the levels of plasma creatinine 24 h after reperfusion compared with vehicle-treated mice (199). In addition, kidneys flushed with and stored in cold Celsior solution supplemented with either CORM-3 or CORM-A1 displayed on reperfusion a higher perfusion flow rate, glomerular filtration rate, and sodium and glucose reabsorption rates compared with control kidneys flushed with Celsior solution alone (172). Interestingly, the respiratory control index from kidney mitochondria treated with CORMs was markedly increased, suggesting that CO may share with biliverdin some beneficial effects on the preservation of

mitochondrial energy metabolism after ischemic events. Additionally, CORM-3 was shown to decrease EC death and restore vascular function (159).

The molecular mechanisms underlying the anti-inflammatory and antiapoptotic effects of CO remain to be fully elucidated. However, a number of studies have shown the possible involvement of the MAPK pathways by CO in preventing inflammatory and apoptotic processes. In this regard, in the presence of 250 ppm CO, LPS-induced activation of the MAPK ERK1/ERK2 and JNK was not affected; however, p38 MAPK activation was significantly increased (143). Furthermore, in an anoxiareoxygenation experimental model, CO exerted its antiapoptotic effects via stimulation of the p38 MAPK pathway (229; Fig. 2).

Bilirubin and Oxidative Stress

Low concentrations of bilirubin scavenge reactive oxygen species (ROS) in vitro, thus reducing oxidant-mediated cellular damage and attenuating oxidant stress in vivo (75). Recently, bilirubin treatment was shown to improve renal vascular resistance, urine output, glomerular filtration rate, tubular function, and mitochondrial integrity after ischemia/reperfusion (I/R) injury and the beneficial effects on kidney viability were achieved most consistently with a dose of 10 μ M bilirubin (13). Although no significant improvement was observed in histological morphology following I/R, electron microscopy of the outer medullary stripe suggested that bilirubin treatment provided a specific protective effect at the level of thick ascending limb demonstrating that mitochondrial integrity (swelling and architecture of cristae) was better preserved in the bilirubin-treated kidneys (13). Consistent with these observations, nanomolar concentrations of bilirubin protected myocardial tissue against I/R injury and both contractile function and mitochondrial integrity were improved following treatment with the bile pigment (34). Bilirubin administration at the time of reperfusion did not attenuate renal I/R injury; however, hemin, a strong HO-1 inducer, ameliorated renal function and

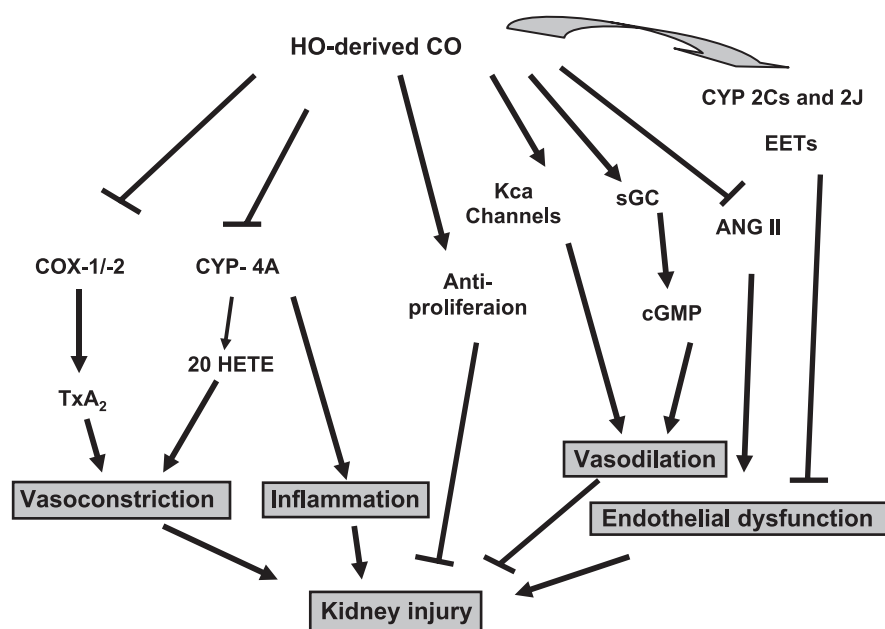


Fig. 2. Figure demonstrates the possible signaling pathways affected by CO. CO activates soluble guanylyl cyclase (sGC), with the resultant increased production of cGMP. CO modulates MAPK, including the p38 MAPK, ERK, and JNK pathways. CO causes a general downregulation of proinflammatory cytokine production through p38 MAPK-dependent pathways leading to anti-inflammatory effects. CO acts to stimulate cGMP but also differs from NO, because CO produces vasodilation by inhibiting vasoconstrictors, including those derived from COX-1/-2 pathways, and activating Kca channels, protects endothelial function, and is both anti-apoptotic and anti-inflammatory. Epoxigenase CYP 2Cs and 2J increase endothelial resistance to dysfunction. EET, epoxyeicosatrienoic acids; HETE, hydroxyeicosatetraenoic acid; COX, cyclooxygenase.

decreased markers of oxidative stress (42). In renal transplant recipients, neither CO gas nor biliverdin normalized the decrease in creatinine clearance and in proteinuria; by contrast, these parameters were normalized by the concomitant administration of CO gas and biliverdin (126). Rats treated with biliverdin before renal transplantation had a significant reduction of macrophage infiltration and of inflammatory markers such as IL-6, IL-1, ICAM-1, and iNOS (126). The effects of biliverdin on iNOS expression and activity are of great relevance; in fact, NO release seems to play a key role during renal I/R injury, since *in vivo* and *in vitro* investigations demonstrated that inhibition of either the expression or activity of iNOS, or the absence of iNOS itself, can ameliorate or prevent renal I/R injury (56).

The biological actions of bilirubin may be of particular relevance to the prevention of the oxidant-mediated vasoconstrictive actions of TNF and ANG II. Bilirubin, in low concentrations, scavenges ROS *in vitro*, reduces oxidant-induced cellular injury, and attenuates oxidative stress *in vivo* (34, 141, 142, 183). The antioxidant and cytoprotective effects of bilirubin in attenuating ANG II-mediated DNA damage and cell death have been described (116). Recently, increased expression of HO-1 resulting in elevated levels of biliverdin/bilirubin has been shown to preserve vascular integrity and prevent EC death and sloughing (178), thus enhancing vascular repairs in diabetic rats (12, 196). Increased HO-1 expression results in increased insulin sensitivity and vascular function (135, 147).

HO System in Diabetic Nephropathy and Kidney Injury

Individuals with diabetes are at risk of developing diabetic nephropathy. Hyperglycemia representing the main cause of increased generation of ROS is also a major cause of chronic kidney disease through the production of oxidative stress and derangement of cell physiology in diabetes mellitus and thus is central in the pathogenesis of diabetic complications. High glucose levels repress HO activity (16, 31, 32) and a decrease in HO activity increased glucose-mediated oxidative stress in the vascular system (9, 44, 110, 154, 188). Consequently, inhibition of HO activity increases the levels of cellular heme and superoxide anion (O_2^-) as well as decreased CO and bilirubin levels, thus exacerbating oxidative stress. A decrease in HO activity resulted in decreased cell survival following exposure to TNF, heme/hemoglobin, or H_2O_2 (4, 35, 92, 220). Decreased HO-1 expression and a decrease in HO activity are seen in type 1 and type 2 diabetes (90, 106, 135), and upregulation of HO-1 attenuates diabetic vascular dysfunction and decrease TNF, IL-1, and IL-6 but increases adiponectin (1).

Renal HO-1 can be induced by several transcriptional factors including Nrf2 to protect the kidney from injury (189). The HO system may be regarded as central in devising a therapeutic approach to arrest the development of diabetic complications including diabetes-related nephropathy by antioxidative and antiapoptotic pathways. Examples of this protective effect in diabetes include the insulin induction of HO-1 through the phosphatidylinositol 3-kinase/Akt pathway and the Nrf2 transcription factor in renal cells (66) and the demonstration that inducers of HO-1 improve insulin sensitivity (54, 111).

Various renal tissues, including mTALH, and the vascular system have the capacity to release ROS in response to various cell injury factors such as glucose, heme, and TNF. In diabetic

rats, impairment of vascular responses, as a result of an increase in O_2^- formation, is a major contributor to vascular injury and the resultant complications of diabetes (14). Gene targeting of human HO-1 gene attenuated glucose-mediated oxidative stress (170). Transgenic cells underexpressing HO-1 showed increased cellular heme content, decreased CO formation, and increased apoptosis and DNA damage. However, overexpression of HO-1 prevented hyperglycemia-mediated apoptosis and cell death and was associated with an increase in the antiapoptotic protein B-cell leukemia-lymphoma-xL (Bcl-xL), an increase in several growth factors, and a decrease in Bad and monocyte chemoattractant protein (MCP)-1 (170).

HO-2 is considered essential in maintaining renal hemodynamics and function. HO-2 was essential in the preservation of normal renal function and morphology (58). HO-2 deficiency in diabetic HO-2 knockout mice resulted in major renal morphological injury and impaired renal function, suggesting that diabetes-induced renal impairment and tubular necrosis was accentuated in streptozotocin (STZ)-treated HO-2^{-/-} mice. Upregulation of HO-1 can compensate for HO-2 deficiency. Upregulation of HO-1 inhibited inflammatory responses, presumably by a decrease in cellular heme-mediated oxidative stress and vasoconstrictors. Consistent with these observations, mice and humans deficient in HO-1 suffer from progressive chronic inflammation and are more sensitive to stressful injury, presumably due to elevated levels of cellular heme and iron (reviewed in Ref. 1).

HO-1 and HO-2 and Acute Kidney Injury

Acute kidney injury (AKI) is enhanced by several factors, including drugs and ischemia, all of which result in increased levels of inflammatory cytokines. These factors activate a number of transcriptional factors, leading to a rapid increase in HO-1 gene expression. HO isoform expression was segmented within the kidney and along the nephron and increased levels of HO-1 inducer suppressed the levels of vasoconstrictor molecules in a tissue-specific manner (22). HO-1 regulates the expression of antiangiogenic CXCL-10 and may alter the critical balance between angiogenic and antiangiogenic factors that is important in the maintenance of the renal microvasculature during injury (41). In a rat model of radiation-induced nephropathy, elevated glomerular HO-1 expression was prevented by treatment with AT₁-receptor antagonists, which block the upregulation of HO-1 expression (127). Renal response to repeated exposure to endotoxin is manifest as AKI, which can be prevented by preconditioning the cytoprotective pathways, via increased levels of HO-1 (128), leading to the conclusion that HO-1 is cytoprotective in the kidney. HO-1 induction exerts a protective effect on renal function in animal models of rhabdomyolysis, cisplatin nephrotoxicity, and nephrotoxic nephritis (127). Further, the products of heme degradation have a protective role in AKI. HO-1-derived CO increased blood carboxyhemoglobin levels, renal blood flow, and glomerular filtration (17). The protective effect of HO-1 on ischemic renal failure is partially mediated by a decrease in the excessive production of NO with a subsequent reduction in peroxynitrite formation observed during ischemia (171).

Gene delivery and pharmacological induction HO-1 in rats attenuate pressor responsiveness to ANG II (198, 221). In the thick ascending limb, the ANG II-mediated increases in oxi-

ductive injury were prevented by selective gene transfer resulting in upregulation of HO-1, thereby blocking inflammation and apoptosis (155). Induction of HO-1 lowered blood pressure (200), and CORMs afforded renal protection against ischemia-induced renal failure (199). Further, induction of HO-1 significantly decreased ANG II-mediated cell injury including renal tubular injury (24). TNF- α -mediated cell death is attenuated by retrovirus delivery of human HO-1 into human microvessels ECs (93). Upregulation of HO-1 provides protection against renal injury following unilateral ureteral obstruction, and this effect is dependent on modulation of the antiapoptotic pathway by perturbation in HO-1 expression (85). HO-1 induction provides resistance in rats to AKI produced by contrast-media; the protective effect was associated with increased antiapoptotic protein levels and decreased expression of pro-apoptotic signals (59). Thus we can infer that the protective effects of the HO system, CO donors, and bilirubin products in AKI are associated with the vasorelaxant, anti-inflammatory, and antiapoptotic effects of the HO system.

In chronic kidney disease, proteinuria serves as a prognostic index of the severity of progressive kidney disease and the rate at which kidney function is lost. MCP-1 increases in the kidney and urine in diverse types of kidney disease (50). MCP-1 is a potent chemoattractant causing chemoattracting effects on leukocytes; induction of transforming growth factor (TGF)-1, a potent fibrogenic cytokine, in resident kidney cells (216); and directly proinflammatory effects on the proximal tubule, in part, by activating NF- κ B (201, 202). In assorted types of chronic kidney disease, the expression of MCP-1 in the kidney and the amounts of MCP-1 in the urine predict the severity of tubulointerstitial disease and the risk for loss of kidney function (224). MCP-1 is upregulated under both unstressed and stressed states in the kidney of mutant mice unable to express HO-1 (131). The expression of HO-1 in the proximal tubule in proteinuric human kidney disease correlated with the severity of proteinuria, hematuria, and tubulointerstitial disease (145). The constitutive overexpression of HO-1 by proximal tubular epithelial cells reduces production of MCP-1 by these cells in response to albumin (125). This suppressive effect involved mechanisms that were distal to the activation of ERK1/2 and were associated with a suppressive effect on NF- κ B activation. Additionally, proteins other than albumin, such as IgG, can also activate NF- κ B and presumably NF- κ B-dependent genes such as MCP-1 in proximal tubules (122). These cytoprotective effects of HO-1 interrupt the progressive loss of renal function in chronic kidney disease.

Induction of HO-1 in the rat by hemin decreased renal levels of TGF- β , a potent profibrogenic cytokine, and suppressed unilateral ureteral occlusion-mediated tubulointerstitial fibrosis, a hallmark of chronic progressive kidney disease (85). Interstitial fibrosis and separation of the tubules were markedly increased after 14 days. Increased HO-1 expression was associated with increased levels of antiapoptotic molecules including Bcl-2 (85). Thus upregulation of HO-1 provided protection against renal injury following unilateral ureteral occlusion and this was dependent on the modulation of the antiapoptotic pathway by HO-1 expression.

A more recent study (82) showed that HO-1 deficiency is associated with increased renal fibrosis and vascular complications. In this study, HO-2^{-/-} mice had significantly more fibrosis compared with wild-type mice. In addition, the extent

of vascular complications was more extensive in obstructed HO-2^{-/-} kidneys, as assessed by smooth muscle actins and expression of S100A4 in proximal tubular epithelial cells. In conclusion, HO-1 deficiency was associated with increased fibrosis, tubular TGF-1 expression, inflammation, and enhanced vascular perturbations in obstructive kidney disease. Modulation of the HO-1 system may, therefore, provide a therapeutic approach to preventing the progression of renal diseases. Indeed, administration of low-dose CO to mice was protective against renal fibrosis (206). The results of this study suggest that low-dose CO exerted protective effects, via the MKK3 pathway, thus inhibiting the development of renal fibrosis in obstructive nephropathy and providing proof of the wisdom of the therapeutic approach.

Effect of HO-1 Interactions with Drug and Growth Factors on Renal Function

The HO system plays an important role in ischemia-mediated injury in organs such as the kidney and brain (187, 194). There is a consensus that heme degradation end products are able to provide tissue protection (15, 219). HO-1/CO induction protected marginal allografts by inhibiting the immunogenicity of donor-derived dendritic cells (93).

The role of the HO system in immunoprotection stems from the observation that atrial natriuretic peptide was an inducer of HO-1 in renal and ECs (83) and thereby caused an examination of this role in the immunoprotection of renal function during the use of cyclosporine (CsA). HO-1 downregulation and upregulation of endothelin-1 by CsA is regarded as a potential mechanism underlying CsA-induced nephrotoxicity (156). Rapamycin has been used in patients at risk of calcineurin inhibitor nephrotoxicity and reduces acute rejection. Recent reports have suggested, however, that rapamycin prolongs graft recovery after ischemic injury through its ability to inhibit protein synthesis and to induce apoptosis ultimately delaying tubular regeneration. Rapamycin increased HO-1 expression in an in vitro model of lung endothelial and smooth cells cultured in the presence of platelet-derived growth factors (204). In addition, the enhanced HO-1 expression was specific to rapamycin, as no induction was observed in the presence of cyclosporine, and it was responsible for rapamycin antiproliferative capacity. Rapamycin delayed renal tubular regeneration and caused increased levels of renal dysfunction in the ischemic renal injury mouse model (57). HO-1 was upregulated after ischemic renal injury, and its expression was enhanced by rapamycin. However, prior induction of HO-1 improved renal dysfunction caused by rapamycin. Upregulation of the protective gene HO-1 partially came the immunosuppressive drug toxicity. The potential mechanisms may be related to phosphatidylinositol 3-kinase (PI3K) and Akt (PKB) activity, but this requires further clarification.

Erythropoietin (EPO) is the major regulator of erythropoiesis and renal function through its inhibition of proapoptotic caspase activation, attenuation of cell death, and signaling molecules (180, 191). HO-1 is phosphorylated by Akt resulting in increased HO-1 activity, and PI3K/Akt-pathway-related responses to oxidative stress and apoptosis have been described at the level of transcriptional regulation of HO-1 (115). The involvement of Akt in the activity of EPO suggests a link between EPO and HO-1. Similar to EPO, simvastatin's anti-

inflammatory and antiapoptotic effects occur through PI3K/Akt induction via HO-1 effects, providing further evidence linking EPO and HO-1 (100). In hemodialysis patients, the enhancement in antioxidant defenses and increased expression of HO-1 seen upon EPO treatment may reflect a high degree of correlation between hemoglobin and HO-1 expression. This suggests a direct nonerythropoiesis-related effect of EPO (25). These reports are consistent with a linkage between EPO, HO-1, and oxidative stress. Carnitine-treated human ECs in culture show increased HO-1 mRNA and protein expression. These results point to a central role for HO-1 as a mediator of EPO and confirm its status as a major antioxidative/antiapoptotic factor. This may confirm a vital role of HO-1 in chronic renal failure patients and vascular disease.

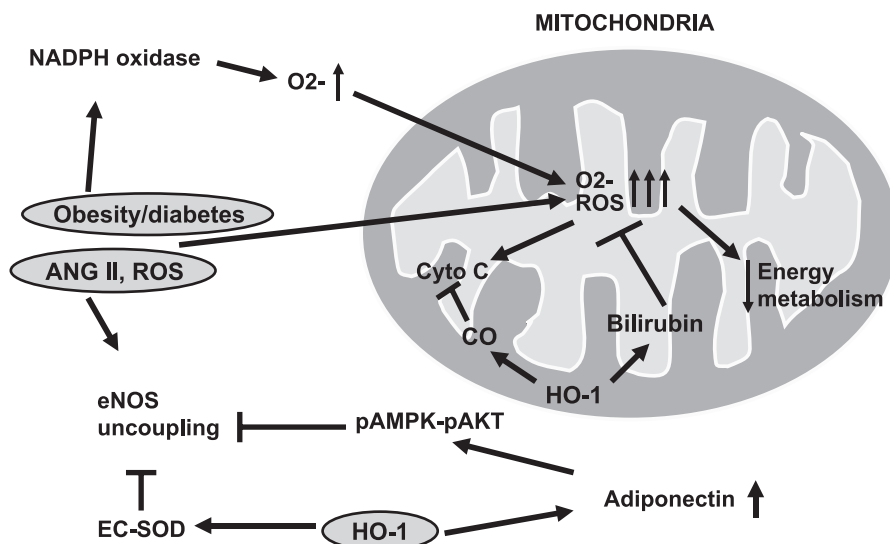
Role of HO in Blood Pressure Regulation

HO-1 expression has been linked to perturbations in blood pressure. Epoxyeicosatrienoic acids (EET) decreases blood pressure presumably through the increased expression of HO-1. In addition, blood pressure elevation in SHR has been shown to occur after renal transplantation from normotensive donors. Furthermore, either acute or chronic administration of stannous chloride, an inducer of HO-1, normalizes blood pressure in SHR rats. Other inducers of HO-1 or HO degradation products decrease blood pressure in SHR and renovascular hypertensive rats (23, 102, 114). HO inhibitors increase systemic arterial pressure even in normotensive rats and magnify myogenic tone in gracilis muscle arterioles. In a similar study, the renal vascular bed lowered blood pressure in hypertension. Heme-induced renal vasodilation, which increased renal blood flow, was a COX-dependant response, whereas heme-induced diuresis and natriuresis were HO-dependant responses, involving inhibition of tubular reabsorption of water and sodium (160). Upregulation of HO activity resulted in the normalization of blood pressure and the increased expression of antiapoptotic molecules in 2K1C renovascular hypertension (139). ANG-II-mediated induction of HO-1 in vitro and in vivo suggests a HO-1 regulatory role in renal protection as recently described in a study of paraquat and ANG II-mediated tubulointerstitial injury and the resultant salt-sensitive hypertension

(150, 193). Furthermore, elevated levels of HO-1 in the renal proximal tubule of rats treated with ANG II was associated with increased HO activity (67). ANG II stimulates oxidative stress via stimulating the generation of both NO (151) and NAD(P)H oxidase-derived superoxide (164), thereby enhancing peroxynitrite formation. ANG II induces endothelial nitric oxide synthase (eNOS) to switch from NO to superoxide production (121). Under pathophysiological conditions associated with renin-angiotensin-aldosterone system overactivation, dysregulation of ANG-II-dependent ROS generation may play an important role in cell oxidation and tissue damage. HO-1 induction lowered blood pressure and superoxide production in the renal medulla of ANG II hypertensive mice (200), which suggested that reduction in superoxide and possibly hydrogen peroxide production in the renal medulla might be a potential mechanism by which induction of HO-1 lowered blood pressure in ANG-II-dependent hypertension. ANG II infusion decreased glomerular filtration rate and increased proteinuria, leading to hypertension. HO-1 upregulation resulted and provided a cytoprotective effect. In addition, systemic inhibition of HO activity increased blood pressure in Sprague-Dawley rats. Also, ANG II promoted mitochondrial ROS production in vascular smooth muscle cells and in rat aorta in vivo (87). As a result of vascular NAD(P)H oxidase activation in bovine aortic ECs, ANG II enhanced mitochondrial superoxide production (49), thus activating redox-sensitive NF-κB, which was followed by stimulation of vascular cell adhesion molecule-1 expression (152).

A possible link exists between ANG-II-related ROS/reactive nitrogen species production and mitochondrial function; thus the regulatory effects of ANG II could be inhibited by antioxidants via the AP-1 signaling pathway (153). ANG II facilitates changes in mitochondrial cytochrome *c* content (99). These results demonstrate that ANG II can depress mitochondrial energy metabolism and that the augmentation of antioxidants due to upregulation of HO-1 may reverse this depression, resulting in amelioration of mitochondrial function (Fig. 3). Additionally, HO-1 translocation into mitochondrial (36, 45) may and have antioxidant effect. Increased levels of HO-1 were accompanied by an increase in adiponectin levels, sup-

Fig. 3. ANG II can stimulate oxidative stress by activating NAD(P)H oxidase-derived superoxide production, and/or by inducing endothelial nitric oxidase synthase (eNOS) uncoupling leading to superoxide production. ANG II can increase mitochondrial ROS generation, resulting in the inhibition of mitochondrial energy metabolism, and a direct interaction between Ang-II and mitochondrial components by-passes activation of NAD(P)H oxidase. Upregulation of HO-1 may inhibit mitochondrial reactive oxygen species (ROS) release, increasing the efficiency of the respiratory chain and protecting mitochondrial structure. In addition, adiponectin appears to have both beneficial and protective effects, which include anti-inflammatory, anti-apoptosis, vasculoprotective and anti-diabetic (69). Adiponectin plays a key regulatory and anti-inflammatory role in the development of hypertension. EC-SOD, extracellular SOD; PI3K, phosphatidylinositol 3-kinase; PPAR, proliferator-activated receptor; SREBP, sterol regulatory element-binding protein; PDK, pyruvate dehydrogenase kinase.



porting the existence of a HO-1-adiponectin axis that is critical in vascular protection (11, 84, 95, 106, 146). Therefore, up-regulation of HO-1, accompanied by an increase in HO activity and the concomitant induction of adiponectin, may play an important role in normalizing hypertension. It has recently been shown that increased levels of NRF-1 occur via an increase in HO-1 expression leading to the gene activation of mitochondria that oppose apoptosis (149).

HO/CO System, 20-hydroxyeicosatetraenoic acid, and EETs

Cytochrome *P*-450 monooxygenases (CYP450) catalyze the metabolism of arachidonic acid (AA) to four EETs, ω/ω -1 alcohols [20-hydroxyeicosatetraenoic acid (20-HETE) and 19-HETE], and six regioisomeric *cis-trans*-conjugated monohydroxyeicosatetraenoic acids (HETEs; Refs. 117, 118). The major CYP450-catalyzed reactions in most tissues are mediated by epoxygenase and ω -hydroxylase activities of the CYP450 family, which are responsible for biosynthesis of 20-HETE and EETs, respectively (29, 119, 163). Some of these metabolites (e.g., 5,6-EET and 20-HETE) can be processed further by COX to products having biological activities (30, 176). Metabolites of AA, via the CYP450 pathway, are endowed with biological activities most relevant to the vascular and renal mechanisms of blood pressure regulation. 20-HETE acts as a vasoconstrictor, whereas 19-HETE functions to increase sodium retention by acting as a potent sodium-potassium-ATPase stimulator. Furthermore, 20-HETE can stimulate contraction of vascular smooth muscle cells (112), inhibit Na^+ - K^+ -ATPase (174), and reduce the activity of potassium channels in arterial smooth muscle and renal tubular cells (211, 231, 232). 20-HETE also affects the movement of ions, constricts blood vessels, participates in tubuloglomerular feedback, and acts as mitogen (109, 233) effects that are prohypertensive. Studies have shown that hypertension is attenuated in SHR through administration of heme arginate, a potent inducer of HO-1 (102), and SnCl_2 (169), a specific inducer of renal HO-1, to demonstrate that increased HO activity, which resulted in depletion of the CYP-AA metabolites 20-HETE and 19-HETE was associated with a reduction in blood pressure. In addition, a single intracardiac injection of retroviral vector containing the human HO-1 gene attenuated the development of hypertension in 5-day-old SHR (166). Administration of heme arginate caused a rapid decrease in blood pressure in young SHR (38, 102, 114). Thus it appears that the antihypertensive effect of HO-1 enhancement may be due, in part, to blunting the vasoconstrictor action of 20-HETE formed via CYP (53, 232, 233). More recently, inhibitors of HO activity have been shown to decrease renal blood flow acutely, implying that the renal HO system supports renal circulation via formation of CO (74, 160, 161). HO-1/HO-2 and CYP450 are expressed in the renal medulla (22, 40, 233), in the arterial and preglomerular arteries (53), and in ECs (2, 104, 105, 226). Upregulation of HO-1 expression by SnCl_2 treatment reduced cortical and inner medullary CYP4A protein levels by inhibiting 20-HETE synthesis (21). Vascular CO counterbalances 20-HETE-mediated vasoconstriction (77). The CO of vascular origin attenuates the sensitivity of renal arterial vessels to vasoconstriction (76). Such interactions may play an important role in the regulation of renal function.

The biological action of HO-1 and HO-2 gene expression suggests their capacity to participate in renal function and blood pressure regulation (76, 166); however, direct evidence to support their involvement in the pathogenesis of hypertension is limited. Renal HO-1 and HO-2 are expressed in most renal structures, and HO-1 is modulated in response to dietary salt, including K^+ (reviewed in Ref. 1). HO-derived CO inhibits the activity of CYP450 (163) and the generation of vasoconstrictive substances, such as 20-HETE, thus ameliorating the development of hypertension and renal function. The ability of CO to reduce the rat renal interlobar arterial sensitivity to phenylephrine and vasopressin is linked to interference with 20-HETE-induced sensitization of the vessels to agonist-induced vasoconstriction (77). The desensitizing action of CO relies on its capacity to stimulate K_{Ca} channel activity in vascular smooth muscle and thereby offsets the inhibitory action of 20-HETE on the K_{Ca} channel, suggesting that the interaction between CO and 20-HETE of vascular origin influences the reactivity of the renal vasculature to constrictor stimuli and thus may contribute to the regulation of renal hemodynamic function (77, 91, 95, 196).

HO-1 derived CO has been shown to regulate vascular tone by decreasing CYP450-derived 20-HETE, vasoconstrictor property (76), and COX-2 activity (61). The interaction of HO-1 gene expression with CYP450 epoxygenase metabolites, EETs, has been reported, and an increase in EET levels was associated with an increase in HO activity in vascular ECs (167, 168). EETs are produced by human liver and kidney CYP450 (97, 177). In rodents, EETs are produced by a member of CYP2C and 2J subfamilies (5, 28, 70, 119, 140). Further, the CYP4A subfamily is responsible for the generation of 20-hydroxyeicosatetraenoic acid, among other HETEs (28, 71, 96, 225). Additionally, HO-1 levels are altered in SHR and induction of this enzyme regulates vascular CYP4A product activity (52, 114, 120, 155, 175).

We previously identified a significant role in the mouse and rat of HO isoforms in regulating renal hemostasis (1, 40, 58, 61) and vascular endothelial COX-2 levels (61). HO-2 gene expression may have a regulatory role in renal function that is masked by HO-1 rapid responses. HO-2 is expressed at high levels in the kidney and is particularly abundant in the renal proximal tubule, the thick ascending limb of the loop of Henle, and the vasculature (3, 21, 23, 39, 40). Mice lacking HO-2 display increased iron accumulation, (43, 58) and increased diabetes-mediated renal injury and circulating creatinine levels (58). Small-interfering RNA selective inhibition of HO-2 activates caspases and increases ROS (195). An increase in ROS has been shown to decrease EET levels (98). Additionally, EET levels are regulated by epoxide hydroxylase.

In nonobese diabetic rats (162), epoxide hydroxylase, the enzyme responsible for the metabolism of EETs to DHETs, is increased. Therefore, it is probable that, in diabetes, the low levels of EETs may be related to an inability to increase HO-1 expression; an increase in ROS, epoxide hydroxylase, and ONOO^- ; and thus an increase 20-HETE and decreasing adiponectin.

A direct link between HO-1 and mitochondrial function has been described previously (45). HO-1 induction is cytoprotective against oxidative stress in the kidney through an increase in the levels of mitochondrial carriers and cytochrome *c* oxidase activity (45) and a decrease in the levels of ROS and EET.

Furthermore, induction of HO-1 in HO-2^{-/-} mice prevents the increase in plasma creatinine levels and tubulointerstitial and microvascular pathology caused by STZ-induced diabetes, indicating that HO activity is essential in preserving renal function and morphology in STZ-induced diabetic mice (58). EET is decreased in diabetic mice (unpublished communication). One final effect of reduced EET levels may be compensated by increased expression of HO-1 and of adiponectin (26). Thus a close correlation exists among EET, HO-1, adiponectin, and NO with positive and negative feedback and alterations in the equilibrium causing diabetic nephropathy. We suggest that the HO system is not the sole of in regulating renal function and include EET along with adiponectin levels. This will implicate the interdependence of three protective circuits, namely HO, EETs, and adiponectin, in the prevention of renal dysfunction, hypertension, obesity, and insulin resistance, the major manifestations of the “metabolic syndrome” (Figs. 2 and 3).

Significance of HO-1 in Vascular Disease and Obesity

Vascular dysfunction is the main cause of many vascular diseases. A child diagnosed with HO-1 deficiency exhibited a growth-inhibited phenotype and extensive endothelial damage (81) and suffered from persistent hemolytic anemia and an abnormal coagulation/fibrinolysis system. Meanwhile, growth retardation, anemia, tissue iron accumulation, and susceptibility to oxidative stress are observed in HO-1 gene-deleted mice. It is apparent that endothelial dysfunction must be recognized as critical in diseases related to decreased levels of HO-1 (218).

Obesity is a chronic inflammatory disease affecting over 72 million adults and affecting women disproportionately (137). Moderate to severe obesity is associated with increased risk for depleted renal function, cardiovascular complications, and insulin resistance in humans (79) and animals (106, 214). In obesity, the kidney is a major target resulting in a series of deleterious actions that include increased renal sodium reabsorption, impaired pressure natriuresis, marked structural changes, loss of nephron function, hypertension, and severe renal injury (for review see Ref. 62).

Obesity is associated with a decrease in HO-1, adiponectin, and EET release. The upregulation of HO-1 in animal models of obesity was associated with a concomitant decrease in the levels of O₂⁻ and iNOS, markers for oxidative stress (84, 90, 106, 135, 146–148). Serum TNF- α , IL-6, and renal macrophage infiltration were increased and adiponectin decreased in several model of obesity. Overexpression of HO-1 resulted in a marked increase in adiponectin levels with a corresponding decrease in levels either of TNF- α , IL-6, and renal macrophage infiltration in animal model of obesity using apolipoprotein A1 mimetic peptide, L-4F, or cobalt protoporphyrin (CoPP) to induce HO-1. HO-1 induction was associated with an increase in the expression of renal pAKT, pAMPK, and peNOS. Thus it appears that the induction of vascular and renal HO-1 in an animal model obesity results in a change of phenotype from pro- to antiapoptotic and acts as an antiobesity and diabetic and improves vascular function (84, 90, 106, 135, 146–148). Increased levels of HO-1 restore kidney function and normalize blood pressure (90, 91).

Increased relaxation has been reported by CORMs but not with the antioxidant heme-degradation product biliverdin (46),

suggesting a potential mechanism involving increased expression of HO-1 resulting in increased production of CO. Recently, we (107) reported that HO-1 upregulation prevents the diabetic state in nonobese diabetic mice. Also, exogenously administered CO and bilirubin prevent EC sloughing in diabetic rats, presumably via a decrease in oxidative stress and, thus, represent a novel approach to prophylactic therapy against vascular damage in patients with diabetes (158). These results, when taken together with those described above, suggest the involvement of CO in protecting against the deleterious effects of a high-fat diet. These results indicated the seminal role of HO-1 in both preventing and reversing hypertension- and obesity-induced endothelial dysfunction in rodents.

Most vascular diseases including hypertension and obesity result from increases in O₂⁻ formation and ROS resulting in the formation of ONOO⁻, which leads to endothelial and beta cell apoptosis and dysfunction (reviewed in Ref. 1). These defects may be reversed by the overexpression of antioxidant enzymes and the administration of antioxidants. Overexpression of HO-1 resulted in decreased O₂⁻ generation, which may be due to a decrease in the levels of NADPH oxidase (94), a heme-dependent protein, and/or an increase in the levels of extracellular SOD (196). Upregulation of HO-1 resulted in a decrease in TNF- α and renal macrophage infiltration. Increased levels of TNF- α contribute to renal inflammation, and TNF- α inhibition reduces renal injury in DOCA-salt hypertensive rats (51). Thus the induction of HO-1 appears to provide an improved cellular environment as a result of favorable antioxidant and anti-inflammatory properties. Indeed, HO-1 overexpression results in an antioxidative, anti-inflammatory, and antiapoptotic phenotype.

Upregulation of HO-1 by the administration of either CoPP or L-4F reduces visceral and subcutaneous adiposity and body weight (84, 106). The mechanism by which upregulation of HO-1 resulted in decreased lipid levels remains unclear. Increased sterol regulatory element-binding protein (SREBP) staining was seen in both SHR and WKY animals fed a high-fat diet that was decreased by CoPP administration. CoPP also decreased the deposition of lipid droplets in the kidney. Hyperlipidemia may mediate renal injury by increasing the expression of SREBP, which is responsible for increasing synthesis of triglycerides and cholesterol in the kidney (Fig. 4). This is associated with the increased expression of TGF- β , VEGF, extracellular matrix proteins, type IV collagen, and fibronectin resulting in glomerular hypertrophy. Further, SREBP stimulates podocyte injury, glomerulosclerosis and tubulointerstitial fibrosis to produce nephropathy (212, 217). These histological changes were observed in SHR animals fed high-fat diets and were prevented by CoPP.

The beneficial effects of adiponectin in a variety of cardiovascular diseases have been reviewed (63, 69), and a negative relationship between adiponectin and hypertension has been proposed (27). Figure 4 describes a proposed mechanistic in the role of HO-1-adiponectin-pAMPK signaling in obesity. The schematic outlines the relationship between HO-1 and its effects on renal function. HO-1 modulates adipocyte function by increasing adiponectin and decreasing IL-6, IL-1, and TNF release (1). Adipocyte-mediated release of adiponectin or adiponectin released from adipocyte within the kidney binds to AdipoR1/R2 receptors mediating the release of LKB-1, acti-

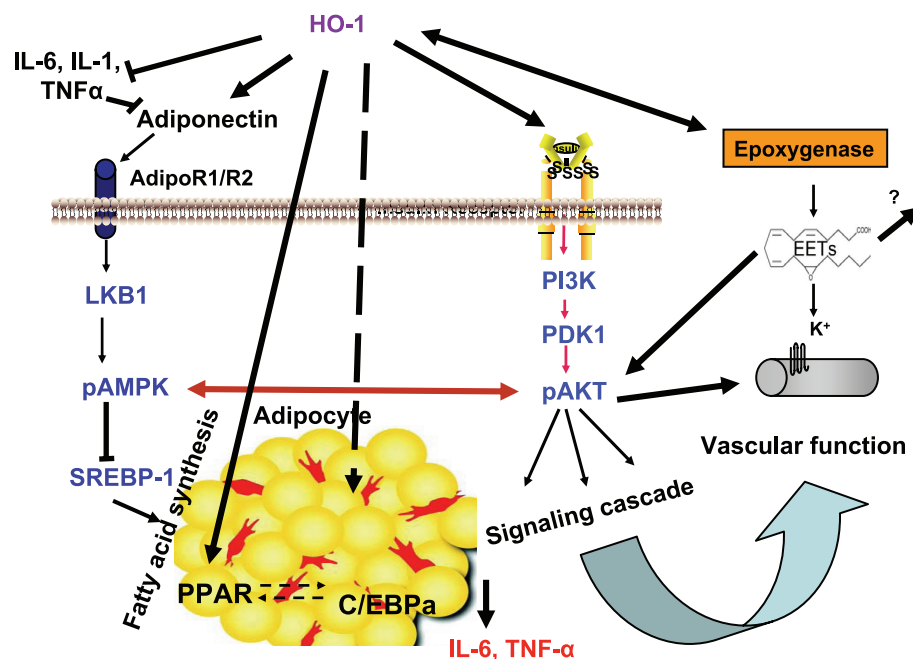


Fig. 4. Schematic diagram for HO-1 modulation of signaling pathway and adiponectin, EET levels, and vascular function. LKB1, serine/threonine kinase; C/EBP α , enhancer binding protein- α .

vation of AMPK, and blockade of SREBP-1, blocking fatty acid synthase and the subsequent generation of fatty acids and LDL. The increase in HO-1 along with adiponectin increases pAMPK-AKT crosstalk and enhances NO bioavailability need for vascular function. EET is shown to increase pAKT (Fig. 4). Additionally, a decrease in renal lipids is also crucial in decreasing oxidative stress and renal injury. Obese African Americans display reduced adiponectin levels associated with albuminuria (179). Adiponectin deficiency in mice is associated with increased oxidative stress, fusion of podocyte foot processes in the kidney glomerulus, and urinary albumin excretion. Adiponectin treatment reversed these abnormalities, possibly through the activation of AMPK. These results suggest a role for adiponectin as a biomarker of kidney disease and a potential target in devising mechanisms for the prevention and treatment of renal insufficiencies (179). Furthermore, serum adiponectin levels are an independent determinant of arteriosclerosis in IgA nephropathy, indicating that manipulation of adiponectin levels may result in the prevention of renal arteriosclerosis and thus protect renal function (72). The elevation of the levels of proteinuria is an important predictor of endothelial dysfunction in early diabetic nephropathy and is known to be associated with lower levels of adiponectin (223). Thus adiponectin may be regarded as both a predictor of and a target for improvement of endothelial dysfunction and prevention of vascular disease.

An increase in renal HO-1 expression was associated with a parallel increase in renal adiponectin and increases in renal eNOS, peNOS, pAKT, and pAMPK (Fig. 4). These changes resulted in an improvement in endothelial function and increased resistance to oxidants and apoptosis. Our results support the report that adiponectin is critical for EC survival and function (144) via the activation of eNOS and pAKT and pAMPK. Activation of AMPK is important in cellular energy homeostasis via stimulation of glucose transport, switching off energy consumption by decreasing lipogenesis, increasing fatty acid oxidation, accelerating glycolysis (113), and inhibiting

triglyceride (215) and protein synthesis (86). An increase in the levels of AMPK reduces inflammation and improves insulin sensitivity and glucose tolerance (19, 222). Both pAMPK and pAKT utilize eNOS as a substrate and enhance the levels of peNOS (1, 33, 47). In addition, AMPK is an important regulator of diverse cellular pathways (64) and is considered to be a “master switch” for cellular energy levels (65). These findings are novel in that they implicate increased HO-1 expression as a key regulator of peNOS levels via an increase in pAMPK and, thereby, result in improved vascular function. In addition, there appears to exist, a temporal relationship between HO-1 and adiponectin in cellular cytoprotection that involves increases in pAMPK, pAKT, and subsequently peNOS and NO availability (1, 135, 147, 148).

Upregulation of renal HO-1 with the resultant increase in signaling molecules including an increase in adiponectin via the pAKT-pAMPK-peNOS pathway prevents metabolic syndrome induced vascular and renal dysfunction. This is manifested by an effect on body weight extends the mechanism by outlining a potential role of the HO-1-mediated increase in adiponectin to control weight gain. The HO-1-mediated increase in adiponectin leads to an improvement in the metabolic syndrome, which, in turn, improves renal function. It is accepted that increases in obesity are considered a risk factor for chronic kidney disease (88, 89). Metabolic syndrome and obesity are characterized by an increase in the levels of inflammatory cytokines such as TNF- α . The clinical significance of these observations in obesity and hypertensive animal models cannot be overstated, as the pharmacological enhancement of HO-1 expression, resulting in a increase in adiponectin, EET, pAKT, pAMPK, and peNOS levels, permits the kidney to initiate a crucial and immediate host defense against metabolic syndrome mediated perturbations in cellular heme due to increased levels of inflammatory cytokines and oxidative stress, thereby preventing the continued deterioration in renal function associated with vascular disease.

HO Induction: Adverse Effects

Accumulating evidence on increased expression of HO-1 has emphasized the cytoprotective effects of the HO system; however, increased levels of HO activity may also have adverse effects depending on the cellular type and environment. Increased HO-1 expression and HO activity promotes vascular endothelial growth factor-mediated endothelial activation and the ensuing inflammatory angiogenesis. Low levels of HO-1 expression are protective, whereas high levels of overexpression worsen cell injury caused by hyperoxia in hamster fibroblasts (185). Prior upregulation of HO-1 by hemin exacerbates I/R injury in the kidney. Inhibition of HO activity by metalloporphyrins either worsens or has no apparent effect on renal injury (127). Furthermore, in high concentrations each of the products of the HO degradation pathway has potential detrimental effects. Bilirubin can be toxic to neural and nonneural cells at high concentrations, and in the newborn hyperbilirubinemia is manifested as neonatal jaundice, kernicterus, and bilirubin encephalopathy (80). CO stimulates mitochondrial generation of free radicals and poisons heme proteins by irreversibly binding the heme moiety (228). Ferrous iron catalyzes free radical reactions (173). Excessive heme-derived CO also promotes endothelium-dependent vasoconstriction by interfering with the NO system (73). Moreover, increased HO activity accelerates tumor angiogenesis and renders tumor cells relatively resistant to anticancer treatment (136). Thus the amount and the site of increased expression of the HO system are crucial to the cytoprotective effects of HO system.

Conclusions

In conclusion, this review summarizes the basic physiology of the HO system; briefly introduces the role of HO system in disease, specifically in renal disease; and suggests a critical role of HO-1 in the protection of renal function. The HO system is involved in many aspects of human physiology, as well as in the pathological circumstances associated with the cardiovascular-renal system and organ transplantation. This is not limited to heme itself but also to its metabolic products, CO, and bilirubin as well as those compounds derived from the wide array of genetic and metabolic processes that are affected when heme metabolism is perturbed. The use of pharmacological and genetic interventions for regulating HO has already provided important new insights into the relation of the heme-HO system to biological and pathological events and offers the potential for development of new therapeutic strategies directed against recalcitrant disease processes. It is, for example, possible to envisage the use of a single drug or gene intervention using site-specific expression to induce long-term prophylaxis against pathological renal events or to promote and enhance repair processes in individuals who have experienced, or are at high risk for, renal injury. These include the adverse effects of hypertension and obesity. As we have discussed above, increased expression of HO-1 can attenuate increased blood pressure levels by depleting thromboxane or regulating COX-1/-2-dependent vasoconstriction and thus improve vascular function. Similarly in obesity, increased levels of HO-1 expression reversed the deleterious effects of the disease. Future research may need to focus on methods of translating the apparent protective properties of the endogenous HO-1 stress response into therapeutic strategies for the treatment of

human disease. Pharmacological and genetic approaches to deliver HO-1 or the end products of heme degradation remain of limited clinical applicability; however, they are worthy of intensive study.

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