

Heme Oxygenase-1: A Potential Antihypertensive Target?

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Abstract: The heme oxygenase (HO) system has received significant attention in recent years as a possible novel target for antihypertensive therapy. HO is the rate limiting enzyme in the metabolism of heme releasing bioactive molecules carbon monoxide (CO) and bilirubin each with beneficial cardiovascular actions. Induction of HO-1 has been demonstrated to lower blood pressure in several animal models of hypertension. In addition to its blood pressure lowering effects, HO can also reduce target organ injury and protect against ischemic injury. Growing experimental evidence suggests that increases in either CO or bilirubin alone may also lower blood pressure and provide protection against hypertensive and ischemic end-organ damage. In this review, we will discuss the current understanding of the actions of the HO on the kidney and cardiovascular systems and how the HO system or its products may be manipulated for antihypertensive therapy.

Key Words: Hypertension, heme oxygenase, carbon monoxide, biliverdin, bilirubin.

INTRODUCTION

It has been over 30 years since the discovery of heme oxygenase (HO) as the enzyme which is responsible for the breakdown of heme [1-3]. During this time, HO has gone from a mundane enzyme responsible for the breakdown of heme to an enzyme involved in several physiological functions including: cell growth and proliferation, regulation of vascular tone, the inflammatory response, and blood pressure regulation. HO is the rate-limiting enzyme in the catabolism of heme into equimolar amounts of ferrous iron, carbon monoxide (CO), and biliverdin (Fig. 1). The ferrous iron produced is rapidly sequestered by ferritin and either pumped out of the cell by an ATPase pump or recycled for heme synthesis, while biliverdin is converted to bilirubin by the ubiquitous enzyme biliverdin reductase.

To date, two main isoforms of HO have been described, HO-1 and HO-2. HO-1, also known as heat shock protein 32, is the inducible isoform. HO-1 is readily induced by an array of stimuli including its substrate heme, heavy metals, ultraviolet light, endotoxin, inflammation, proinflammatory cytokines, shear stress, hypoxia, hyperoxia and other oxidants [4]. HO-2 is constitutively expressed in many organs with the highest levels observed in the brain and testes [5]. HO-3 is an alternative isoform found exclusively in rats; it has no heme catalytic activity and is not considered a source of CO or biliverdin production *in vivo* [6].

Traditionally, HO metabolites CO and bilirubin have been considered to be toxins with deleterious physiological actions (Table 1). CO is known for its toxicity during exposure to exhausts from the combustion of fossil fuels and wood, while severe jaundice in newborns (kernicterus) is a consequence of unconjugated hyperbilirubinemia. Given these facts, the HO system would seem to be an unlikely

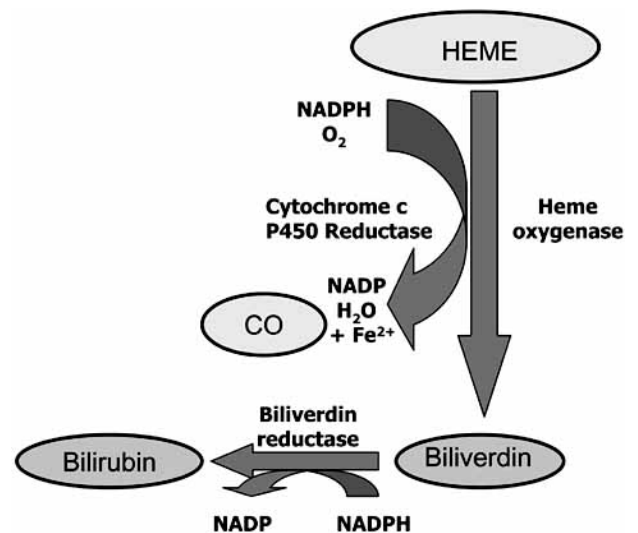


Fig. (1). Overview of the heme oxygenase (HO) system. Heme oxygenase metabolizes heme and in the process generates ferrous iron (Fe^{2+}), carbon monoxide (CO), and biliverdin. Biliverdin is rapidly converted to bilirubin *via* the ubiquitous enzyme biliverdin reductase.

candidate for antihypertensive therapeutic applications. However, recent experimental evidence has demonstrated the important role of the endogenous HO system in the regulation of numerous cardiovascular functions which may support a role for this system in the regulation of blood pressure. First, induction of HO-1 either pharmacologically or genetically prevents hypertension in various animal models of the disease [7-10]. Second, HO-1 is induced by angiotensin II (Ang II), suggesting that upregulation of this enzyme might be one of the body's defense against Ang II-dependent hypertension [11,12]. Finally, mice lacking HO-1 have a greater hypertensive response to renovascular, one kidney, one clip, Goldblatt hypertension [13]. Taken together these studies suggest that HO-1 may be a potential target for antihypertensive therapy.

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Table 1. Beneficial and Pathological Actions of HO-1 Metabolites

Metabolite	Beneficial	Pathological
Carbon Monoxide (CO)	Anti-inflammatory, Anti-apoptotic, Vasodilator, Antioxidant	CO poisoning, Heme Binding
Bilirubin	Antioxidant	Jaundice
Iron (Fe ²⁺)	Induction of Ferritin	Potent Oxidant

HO AND RENAL TUBULE FUNCTION

Computer models and experimental evidence strongly support a central role for the kidneys in the long-term regulation of body fluid volume and arterial pressure [14,15]. The kidney responds to an increase in mean arterial pressure (MAP) by increasing sodium and water excretion, a phenomenon known as renal pressure-natriuresis. The increase in sodium and water excretion reduces blood volume and cardiac output until MAP falls all the way back to normal in an infinite gain response [16]. Conversely, if MAP falls below the normal setpoint, the kidneys respond by conserving sodium and water until MAP is raised back to normal levels. The pressure-natriuretic response has been reported to be shifted towards higher pressures in all models of hypertension that have been examined [17]. While hormones and paracrine agents such as angiotensin II, nitric oxide, cytochrome P450 metabolites of arachidonic acid, and prostaglandins are known modulators of pressure-natriuresis, the mechanism responsible for resetting of pressure-natriuresis in hypertension is currently unknown.

The role of HO in the regulation of sodium reabsorption is controversial with some studies indicating the increases in HO activity increase sodium reabsorption and others suggesting a natriuretic role for increases in HO activity. HO-derived CO has been reported to stimulate the 70 pS K⁺ in the TALH [18]. This K⁺ channel is important in maintaining the lumen-positive transepithelial potential and recycling K⁺ ions for the sodium, potassium, 2 chloride (NKCC) transporter in the thick ascending loop of Henle (TALH). Further studies utilizing *in vivo* microperfusion of superficial loops of Henle have demonstrated that inhibition of HO with chromium mesoporphyrin (CrMP) results in a decrease in sodium and fluid reabsorption [19]. In contrast, induction of HO-1 with heme increases urine volume and sodium excretion without increasing glomerular filtration rate [20]. One possibility for the apparent discrepancy in these results could be the different isoforms of HO that are expressed in renal medulla under basal conditions and after hemin treatment. It is possible that HO-1 and HO-2 can produce different levels of CO and bilirubin which may have different effects on sodium handling in the kidney. Another potential explanation for these results is that the acute inhibition of HO leads to decreases in CO which increase nitric oxide production as well as inhibits the 70 pS K⁺ channel to decrease sodium reabsorption; however, when HO-1 is induced it may produce CO and bilirubin in excess to alter sodium reabsorption *via* a mechanism dependent on tubular oxidative stress levels.

Increased oxidative stress has been shown to contribute to the development of hypertension. For example, several studies utilizing isolated, perfused TALH tubules have dem-

onstrated that superoxide (O₂⁻) can stimulate sodium reabsorption in this tubule segment either *via* a direct activation of the NKCC transporter or through decreasing the bioavailability of nitric oxide [21,22]. Experiments to localize NADPH oxidase in the nephron have found the highest concentrations to be in TALH [23]. Further studies have demonstrated that increases in O₂⁻ production in the renal medulla can increase blood pressure in normotensive rats and may be involved in salt-sensitive hypertension in the Dahl salt-sensitive (Dahl S) rat [24,25]. Experiments on medullary microtissue strips have also demonstrated that Ang II can increase O₂⁻ production through the stimulation of NADPH oxidase [26]. This increase in Ang II-mediated superoxide production can contribute to hypertension by increasing sodium reabsorption in the thick ascending loop of Henle directly and through inhibition of nitric oxide (Fig. 2).

The increase in superoxide production can further inhibit the pressure-natriuretic response through increased renal vasoconstriction. Recent evidence from our laboratory shows that induction of HO-1 with cobalt protoporphyrin (CoPP) prevents the development as well as lowers blood pressure in established Ang II dependent hypertension. The reduction in blood pressure with HO-1 induction is associated with a decrease in O₂⁻ levels in the renal medulla of Ang II treated mice [27]. While the mechanism for decreased Ang II mediated O₂⁻ levels in the renal medulla of CoPP treated mice is unknown, it is possible that increases in CO or bilirubin directly decrease Ang II stimulated NADPH oxidase activity which could reduce sodium reabsorption in the TALH and attenuate renal vasoconstriction [28,29] (Fig. 2). Alternatively, it is possible that induction of HO-1 increases the antioxidant capacity of tubule cells through proteins such as superoxide dismutase and catalase [30].

HO AND VASCULAR FUNCTION

HO-2 is the main isoform expressed in the vasculature under basal conditions [31,32]. However, HO-1 can be induced in vascular smooth muscle cells by several stimuli including metals, hypoxia, and endotoxemia [33-35]. HO derived CO causes vasodilatation by both activating soluble guanyl cyclase (sGC) and by activation of high conductance Ca²⁺ activated K⁺ channels [36-38]. CO has been demonstrated to be an important vasodilator in several tissues, including the brain, heart, lung, and kidney [37,39-42]. In the renal vasculature, CO serves to buffer against Ang II and phenylephrine induced vasoconstriction [43]. Recent studies have demonstrated that induction of HO-1 or treatment with carbon monoxide releasing molecules (CORMs) can improve Ach-mediated relaxation in diabetes [44]. Bilirubin has been reported to improve endothelial-dependent vascular relaxation in high fat fed LDL receptor knockout mice [45].

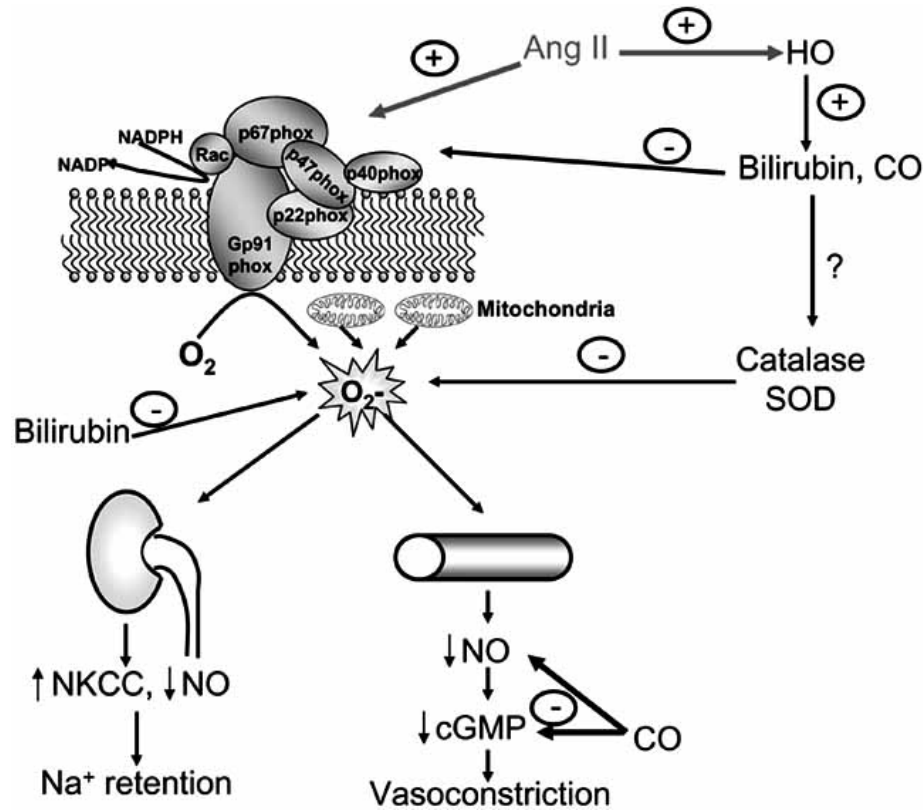


Fig. (2). HO, Ang II, and superoxide production. Ang II acts to stimulate the activity of the NADPH oxidase which increases the cellular levels of superoxide. The increased superoxide can then increase blood pressure by increasing sodium reabsorption in the kidney directly and by inhibition of nitric oxide. Superoxide can also diminish nitric oxide signaling in vascular smooth muscle cells (VSMC) leading to enhanced vasoconstriction. HO metabolites, CO and bilirubin, can directly inhibit the NADPH oxidase to decrease superoxide production. Bilirubin also has direct antioxidant effects as well. CO increases cGMP levels in VSMCs and increases endothelial nitric oxide synthase which can attenuate increased vasoconstriction. Bilirubin and CO may also lead to increases in antioxidant proteins such as superoxide dismutase (SOD) and catalase which further act to decrease superoxide levels in the cell.

There is a complex relationship between HO and nitric oxide (NO) in the vasculature. Previous studies have shown that low levels of CO (0.001-0.1 $\mu\text{mol/L}$) can stimulate NO release while higher levels of CO ($\geq 1 \mu\text{mol/L}$) inhibit nitric oxide synthase [46]. In diabetic animals induction of HO-1 induces eNOS levels and improves relaxation to acetylcholine [30,47]. However, transgenic mice overexpressing human HO-1 cDNA under the control of the smooth muscle specific SM22-alpha promoter have impaired NO-dependent relaxation and hypertension. These mice also exhibit an attenuated cGMP response to NO which is restored upon inhibition of HO [48]. Recent studies by Johnson and colleagues have indicated that increased production of CO is linked to alterations in vascular function in models salt-sensitive hypertension and obesity [49,50]. In these models, acute inhibition of HO improves arteriolar dilation in response to acetylcholine as well as lowers blood pressure. Thus, it appears that although HO and its metabolites can have many beneficial effects on the vasculature, excessive amounts of CO may actually lead to endothelial dysfunction, particularly in salt-induced hypertension or obesity.

HO AND INFLAMMATION IN HYPERTENSION

There is considerable evidence that hypertension might be at least in part an inflammatory disease [51,52]. Evidence

of chronic low grade inflammation has been identified as an integral part in the pathogenesis of hypertension either as a primary or secondary event. Clinical studies have demonstrated that hypertensive individuals have increased pro-inflammatory markers, such as high sensitive C-reactive protein (hsCRP) even after adjustment for potential confounding factors. Furthermore, elevated hsCRP levels have also been shown to predict the development of hypertension in pre-hypertensive and normotensive patients [51]. Hypertension is also linked to other well recognized inflammatory conditions such as Systemic Lupus Erythematosus [53]. Inflammation has been implicated in both endothelial dysfunction and arterial stiffness in the pathophysiology of hypertension. Further, there is some evidence that drugs commonly used in the management of hypertension, such as statins, angiotensin converting enzyme inhibitors and Ang II receptor blockers have anti-inflammatory properties that can positively influence outcomes in patients with hypertension [51].

There are several studies which suggest that HO-1 has significant anti-inflammatory properties through the production of either CO or bilirubin [54-57]. Studies in cultured macrophages have demonstrated that both induction of HO-1 as well as increased levels of CO can prevent lipopolysaccharide induced increases in inflammatory markers including

iNOS and tumor necrosis factor- α [58,59]. Induction of HO also limits macrophage infiltration in models of renal injury [60,61]. HO-1 has also been reported to reduce inflammation in models of pulmonary and portal hypertension [62,63]; however, its anti-inflammatory role in obesity induced or essential hypertension has yet to be explored.

HO AND HYPERTENSIVE TARGET ORGAN INJURY

Hypertension is associated with an increased risk for stroke, heart disease, and kidney failure. Protection from hypertension-induced end organ damage is a highly significant clinical problem, especially in patients whose blood pressure is difficult to control with standard anti-hypertensive therapies. Targeting the HO system may have potential therapeutic value to protect against hypertension-induced end organ damage independent of blood pressure lowering effects of HO induction. Induction of HO-1 can protect the kidney from injury caused by ischemia, nephrotoxins, and rhabdomyolysis [64-66]. Human HO-1 deficiency is associated with persistent proteinuria, tubular atrophy, and marked inflammatory cell infiltration of the kidney [67]. Experimental evidence also demonstrates that increased HO-1 can protect the kidney from Ang II-induced renal damage [12]. However, the induction of HO-1 with heme also lowers blood pressure making it difficult to determine if the protective effects of HO-1 induction are independent of the lowering blood pressure. Studies on isolated thick ascending loop of Henle cells have demonstrated that induction of HO-1 can protect against Ang II-mediated oxidative injury [68]. Similar results were observed in endothelial cells suggesting that the anti-oxidant actions of HO-1 induction may be in part responsible for protecting against kidney injury [69]. Whether the protection afforded the kidney from HO-1 induction is due to increased CO, bilirubin or both is not known. Both CO and bilirubin have been reported to protect the kidney against ischemia-induced renal injury [60,70,71]; however, the ability of these metabolites to protect against hypertensive end organ injury has not been examined.

There is abundant evidence that HO and its metabolites can protect the heart from ischemic damage. This is especially relevant given the increased risk of myocardial infarction in patients with hypertension. Studies in HO-1 gene knockout mice as well as transgenic mice specifically overexpressing HO-1 in cardiomyocytes have demonstrated the protective actions of HO-1 against ischemic injury following acute myocardial infarction [72,73]. These reports are consistent with findings in humans that a promoter variant of the HO-1 gene which increases HO activity is associated with a decreased incidence of ischemic heart disease in a Japanese population [74]. Experiments using CO inhalation or carbon monoxide releasing molecules have demonstrated the ability of CO to limit infarct size and preserve cardiac function following acute myocardial infarction [75-78]. While the precise mechanism for the protective actions of CO against myocardial infarction has yet to be identified, p38MAPK, Akt, eNOS and L-type Ca^{2+} channels have been proposed as targets which may mediate the protective actions of CO [79,80].

HO may also protect against cardiac hypertrophy. In both genetic models and Ang II-dependent hypertension, chemical

induction of HO-1 was able to attenuate the development of cardiac hypertrophy independent of a measurable reduction in blood pressure [81,82]. Further, in isolated cardiomyocytes, induction of HO-1 as well as treatment with either CO or bilirubin alone decreased extracellular signal-regulated kinases (ERK1/ERK2) and p38 mitogen-activated protein kinase (MAPK) activation and inhibited the prohypertrophic calcineurin/NFAT pathway [83]. However, a recent study found that overexpression of HO-1 in cultured myocytes resulted in a decrease in Ang II-mediated apoptosis but not hypertrophy [84]. It is clear from these studies that further research into the potential role of HO-1 and its metabolites in the protection against hypertension induced cardiac damage is warranted.

TARGETING HO AND ITS METABOLITES FOR THE TREATMENT OF HYPERTENSION AND TARGET ORGAN INJURY

Despite animal studies which strongly suggest the potential beneficial effects of the HO system to lower blood pressure and protect against target organ injury, the translation of these studies to human hypertension is still in its infancy. The benefits of HO induction in the cardiovascular system are not limited to its antihypertensive effect. HO-1 may also have a role in preventing hypertensive target organ damage as discussed above. The HO system can be potentially manipulated on several levels to lower blood pressure. Strategies in which HO enzymes or the products of HO, CO and bilirubin, are targeted may offer viable options for anti-hypertensive therapies. The benefits and limitations of each strategy are summarized in Table 2 and discussed in detail below.

HO-1 Induction

As mentioned earlier, HO-1 can be induced by an array of stimuli such as its substrate heme, heavy metals, ultraviolet light, endotoxin, inflammation, shear stress, and hypoxia. The challenging task is to identify a safe means to specifically induce HO-1 in a target organ for extended periods of time. One of the leading candidates is Hemin which in the form of the drug, hematin, is used for the treatment of acute porphyria [85,86]. Hemin is a strong inducer of HO-1 and its administration has been previously demonstrated to lower blood pressure in the spontaneously hypertensive rat but not in normotensive controls [87]. The effects of hemin on blood pressure have been mainly studied acutely in younger animals before the onset of hypertension. An important recent study has demonstrated the long-term blood pressure lowering effects of hemin treatment in hypertensive rats [88]. In this study, treatment of SHR with a hemin containing minipump for 3 weeks not only lowered blood pressure acutely, but these effects lasted up to 9 months after removal of the hemin minipump. The sustained decrease in blood pressure was associated with a constant induction of HO-1 and endothelial nitric oxide synthase (eNOS) in mesenteric arteries of hemin treated rats [88]. The sustained decrease in blood pressure with hemin was not associated with any change in body weight or markers of hepatotoxicity such as alanine aminotransferase (ALT) or γ -glutamyltranspeptidase (γ GT). The results of this study indicate that hemin treatment may be a feasible approach to test the blood pressure lowering effects of HO-1 induction in humans.

Table 2. Antihypertensive Targets of the HO System

Target	Method	Benefit	Limitation
HO-1	Hemin, Gene Therapy	Anti-hypertensive, Protective Against Target Organ Injury	Excessive Fe ²⁺ and CO
CO	Carbon Monoxide Releasing Molecules (CORMs)	Vasodilator, Anti-apoptotic Anti-oxidant, Protective Against Ischemic Injury	Chronic Delivery of Compounds
Bilirubin	UGT Antagonism, Local Delivery	Antioxidant	Inhibitors of UGT, Ability to Target Specific Tissues/Cells

HO-1 gene therapy is a potential alternative for direct HO-1 induction to in the treatment of hypertension. Several studies have demonstrated that treatment of young SHR with a lentivirus overexpressing HO-1 can prevent the development of hypertension [89,90]. Lentivirus and recombinant Adeno-associated virus have the unique properties of infecting non-dividing cells of which the kidney is mainly composed. There are several areas of concern with the use of these viral vectors in humans which limits their current use. The main limitation is the random integration in the genome observed with lentiviruses. This is not an issue with adeno-associated viruses and there are alternative strategies to achieve site-specific integration in mammalian genomes which can also be utilized in the future [91]. As research on human gene therapy for hypertension progresses, HO-1 should be a leading candidate for anti-hypertensive gene therapy given its success in animal models of hypertension. However, unabated overexpression of HO-1 is not without potential adverse actions due to the potential for iron release and effects on other heme containing proteins [92]. Given this possibility, an ideal level of HO-1 overexpression must be obtained in which the maximum protective effects of HO-1 are realized and the potential deleterious effects avoided.

An alternative HO-1 gene therapy strategy which could be used to treat both hypertension and end organ damage is to link HO-1 expression with specific pathological stimuli. This approach could allow for rapid induction of HO-1 in response to increases in pressure, shear-stress, or hypoxia. This strategy has been successfully incorporated to protect the heart against ischemic injury by linking the expression of HO-1 directly to a hypoxia-inducible promoter [93,94]. In these studies, the expression of HO-1 was under the control of an oxygen-dependent degradation domain from the hypoxia inducible factor-1-alpha. This allows for specific, rapid induction of HO-1 in the areas of ischemia for entire timeframe of the ischemic episode. The expression of HO-1 was then elegantly turned off after resolution of the ischemia [94]. The regulation of HO-1 in this matter was associated with a preservation of cardiac function and attenuating left ventricle remodeling [94]. As further advances are made to identify genes which can specifically respond to changes in physical factors such as pressure, flow, and alterations in ion concentrations, these genes could then be used to direct specific expression of HO-1 in direct response to pathologic stimuli for maximum protective effects.

Carbon Monoxide Releasing Molecules (CORMs)

CORMs are recently developed compounds which have the ability to liberate CO under physiologic conditions[95]. These compounds have been demonstrated to be protective against ischemia in both the heart and kidney [71,75,76]. Another benefit of these compounds is their ability to increase the local levels of CO without significant increases in blood carboxyhemoglobin which are often observed with CO inhalation therapy [71]. CO is a known vasodilator and may also have direct natriuretic actions in the kidney. These properties make it a potentially novel anti-hypertensive candidate.

The greatest limitation with the use of CORMs as a potential anti-hypertensive therapy is the short half-life of the compounds which limits their use in chronic animal settings and makes it difficult to perform the studies needed to effectively evaluate these compounds as potential anti-hypertensive therapies [96]. Secondly, the first generation CORMs are metal containing carbonyl compounds [95]. The metal group of these compounds can induce HO-1 which could lead to further increases in CO and bilirubin independent of the actions of the CORMs [71]. This would make it difficult to determine the direct effects of CO from the secondary effects of HO-1 induction. To circumvent this problem, these studies should be performed with CORMs which lack the metal complex to avoid direct induction of HO-1[96]. However, as stated above, CORMs which lack the metal containing group have shorter half-lives than their metal containing counterparts, thus limiting their use chronic animal settings. The development of more stable CORMs will be needed to further advance the study of the anti-hypertensive properties of CORMs.

Bilirubin

The breakdown of the heme prosthetic group by HO yields biliverdin which is rapidly converted to bilirubin by the enzyme biliverdin reductase. Biliverdin reductase is a ubiquitous enzyme responsible for the conversion of biliverdin to bilirubin. Bilirubin has little solubility in water whereas biliverdin is water soluble. Hepatocytes utilize the enzyme uridine-diphosphate-glucuronosyltransferase 1A1 (UGT1A1) to add 2 equivalents of glucuronic acid to bilirubin to produce the more water soluble bilirubin diglucuronide derivative which is excreted into the bile salts. Genetic mutations

in the UGT1A1 gene in humans (Crigler-Najjar or Gilbert's syndrome), which reduce the activity of the enzyme, lead to increased levels of unconjugated bilirubin. The homozygous Gunn rat, which lacks the equivalent enzyme, uridine diphosphate glucuronyltransferase (UDPGT), is an animal model of Crigler-Najjar syndrome which was found to be resistant to the pressor effect of Ang II [97]. Also, increased levels of unconjugated bilirubin in the plasma have been associated with lower blood pressure in pre-eclamptic women [98]. This raises the possibility that increases in plasma levels of unconjugated bilirubin may lower blood pressure in hypertensive individuals. It is known that treatment with phenobarbitone can induce UGT1A1 but there are no specific inhibitors of the enzyme at the present time. However, UGT1A1 glucuronates bilirubin and xenobiotics in a reaction which follows different kinetics depending on the substrate [99]. When drugs that are metabolized by UGT1A1 are administered at sufficient quantities, the enzyme may become saturated leading to increases in unconjugated bilirubin levels. It may be possible that a physiologically inert drug glucuronated by UGT1A1 could be used to competitively inhibit bilirubin conjugation and increase bilirubin levels in the plasma. Such a drug could be administered to hypertensive individuals and its effects on plasma bilirubin levels and blood pressure monitored. Currently, drugs such as Indinavir and p-Nitrophenyl, which are known inhibitors of UGT1A1 could be investigated for antihypertensive properties through increases in unconjugated bilirubin levels. Ideally, the goals of these types of studies would be to determine if raising unconjugated bilirubin in the plasma sufficiently to lower blood pressure could be achieved at levels that would not be associated with jaundice or alterations in liver function.

While there is evidence that increases in unconjugated plasma bilirubin may lower blood pressure [98,100], the role of increased tissue levels of bilirubin in the prevention of hypertension and end organ injury has yet to be examined. One reason is the inability to alter the levels of bilirubin independent of HO and CO in the cell. One option is to selectively target biliverdin reductase in order to decrease cellular bilirubin generation. However, biliverdin itself has antioxidant capabilities [101], and recent studies have demonstrated that biliverdin reductase is a serine/threonine kinase that contains a bZip domain which may be capable to regulate expression of genes such as activating transcription factor 2 and HO-1 [102]. The ability of increased tissue levels of bilirubin to lower blood pressure will ultimately have to be determined by local, tissue specific delivery of either bilirubin or biliverdin in hypertensive animal models.

PERSPECTIVES

It is clear that the HO system through direct actions as well as through the actions of the main metabolites, CO and biliverdin/bilirubin, may afford the opportunity for the development of novel antihypertensive therapies. Furthermore, this system is also a good candidate for the development of therapies to ameliorate hypertension induced target organ injury. In the next years, further animal studies will be needed to evaluate the efficacy of CO or bilirubin therapy to lower blood pressure in different models of hypertension. It may be necessary to develop novel methods to deliver these

compounds in a tissue specific fashion in order for the maximum beneficial effects of these metabolites to be realized. HO-1 gene therapy may also be a novel approach to combat human essential hypertension if the dose of the gene can be titrated to achieve maximal positive effects and limit potential deleterious effects. Overall, the HO system offers many potential benefits against cardiovascular disease that need to be further explored.

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