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Physiological significance of heme oxygenase in hypertension

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Abstract

The last decade has witnessed an explosion in the elucidation of the role that the heme oxygenase system plays in human physiology. This system encompasses not only the heme degradative pathway, including heme oxygenase and biliverdin reductase, but also the products of heme degradation, carbon monoxide, iron, and biliverdin/bilirubin. Their role in diabetes, inflammation, heart disease, hypertension, transplantation, and pulmonary disease are areas of burgeoning research. The research has focused not only on heme itself but also on its metabolic products as well as endogenous compounds involved in a vast number of genetic and metabolic processes that are affected when heme metabolism is perturbed. It should be noted, however, that although the use of carbon monoxide and biliverdin/bilirubin as therapeutic agents has been successful, these agents can be toxic at high levels in tissue, e.g., kernicterus. Care must be used to ensure that when these compounds are used as therapeutic agents their deleterious effects are minimized or avoided. On balance, however, the strategies to target heme oxygenase-1 as described in this review offer promising therapeutic approaches to clinicians for the effective management of hypertension and renal function. The approaches detailed may prove to be seminal in the development of a new therapeutic strategy to treat hypertension.

Keywords

Heme oxygenase; Hypertension; Carbon monoxide; Bilirubin; Adiponectin

1. Introduction

Heme oxygenase (HO), comprising HO-1 and HO-2, functions as the rate-limiting enzyme in the degradation of heme, a process that leads to formation of equimolar amounts of the bile pigment biliverdin, free iron and carbon monoxide (CO). Biliverdin formed in this reaction is rapidly converted to bilirubin. Heme oxygenase has been reported to be present in all tissues and is located in microsomes (Abraham and Kappas, 2008). Recently HO-1 and HO-2 have been shown to be also present in mitochondria (Di Noia et al., 2006; Turkseven et al., 2007). It is now apparent that HO-2 is constitutively expressed, whereas HO-1 is inducible by a large number of structurally unrelated pharmacological and other agents as well as by a variety of circumstances, that include heat shock and both cellular and oxidant stress. The HO system provides both antioxidant and anti-apoptotic properties due to its byproducts, bilirubin/biliverdin and CO, respectively (Abraham and Kappas, 2008) (Fig. 1). HO-1 is induced by oxidant stress and plays a crucial role in protection against oxidative insult in diabetes and cardiovascular diseases (Abraham and Kappas, 2008).

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A spectrum of drugs have been used to up-regulate HO-1 expression and HO activity. Stannous chloride (SnCl_2) has been reported to lower blood pressure in spontaneously hypertensive rats (Sacerdoti et al., 1989). Metalloporphyrins, such as heme, heme arginate, and CoPP, are also commonly used drugs to induce HO-1 expression and HO activity and have been used to normalize blood pressure in animals and humans (Kordac et al., 1989; Levere et al., 1990; Abraham and Kappas, 2008). However, in discovering the ideal pharmacological drug, one must consider the dose and time of HO-1 induction. Therefore, most of the pharmacological inducers of HO-1, such as hemin and heavy metals, used in experimental studies may show cellular and tissue toxicity if used at high concentrations. Thus, the adverse and long-term effects of increased HO-1 expression and its effect on the heme synthesis pathway must be elucidated before clinical application. Aspirin is known to reduce the incidence of thrombotic occlusive events, such as myocardial infarction and stroke. Aspirin increased HO-1 protein levels and HO activity in a dose-dependent manner in cultured endothelial cells derived from human umbilical vein. Pretreatment of cells with aspirin or bilirubin protected endothelial cells from H_2O_2 -mediated toxicity (Abraham and Kappas, 2008). Another type of drug, statins, the widely used lipid-lowering agents, substantially decrease cardiovascular morbidity and mortality in patients with and without coronary disease. Simvastatin and lovastatin increase HO-1 mRNA levels in cultured endothelial cells derived from human umbilical vein (Abraham and Kappas, 2008). Recently, we reported that L-4F and D-4F mimetic peptides increased levels of aortic HO-1 protein, HO activity, and extracellular superoxide dismutase while decreasing superoxide levels (Abraham and Kappas, 2008; Peterson et al., 2007). Probucol, an antioxidant drug, reduces the risk of restenosis. The protective effect of probucol depends not only on its ability to inhibit lipid oxidation but also on its ability to induce HO-1. Treatment with paclitaxel, possessing antiproliferative effects on vascular smooth muscle cells, resulted in a marked time- and dose-dependent induction of HO-1 mRNA, followed by corresponding increases in HO-1 protein and HO activity (Choi et al., 2004). It has been suggested that HO-1, induced by rapamycin in VSMCs, shows an antiproliferative effect, resulting in the reduction of the restenosis rate (Abraham and Kappas, 2008). Resveratrol, an important component in certain varieties of red grapes, generates cardioprotection by preconditioning the heart via a HO-1-mediated mechanism. Most studies use metalloporphyrins, CoPP and heme arginate to increase the levels of HO-1 proteins and HO activity. In this review, we will focus on these compounds as they can be considered as “model” inducers of HO-1.

Upregulation of HO-1 gene expression prevents vascular dysfunction and endothelial cell death through a decrease in ROS levels (Abraham and Kappas, 2008). The acute induction of HO-1 has been shown to have a beneficial effect due to the rapid decrease in the undesired pro-oxidant heme. Sacerdoti et al. (1989) first reported the benefits of an acute effect of increased levels of HO-1 protein demonstrating that SnCl_2 treatment prevented the development of high blood pressure. Subsequently, others reported that acute and chronic expression of HO-1 decreased vasoconstrictors, such as 20-HETE (Abraham and Kappas, 2008), thromboxane synthase activity (Abraham and Kappas, 2008) and COX-2 activity (Abraham and Kappas, 2008). Heme arginate caused an acute induction of HO-1 resulting in lowered blood pressure in hypertensive rats (Wu and Wang, 2005; Abraham and Kappas, 2008; Schwartzman et al., 1990). Chronic induction of HO-1 by low concentrations of cobalt protoporphyrin (CoPP), moderately decreased cellular heme content and cytochrome P450 levels and increased eNOS, phosphorylated AKT (pAKT) and endothelial cell survival in diabetic rats (Wu and Wang, 2005; Abraham and Kappas, 2008) and SHR. Chronic administration of small doses of CoPP, attenuated the coronary constrictor response to ischemia-reperfusion (L'Abbate et al., 2007). The role of HO-2 in cells is not as well understood; however, it is becoming apparent that HO-2 may have an important role in epidermal cells, germ cell development and signal transduction in neural tissues. CO is an activator of sGC and it has been suggested that it may be a major physiological regulator of cGMP levels in the brain (Wu and Wang, 2005). HO-2 has been found to be closely associated with sGC, ALA synthase, cytochrome P450 reductase and NOS

in the brain (Wu and Wang, 2005). It has been suggested that, in the brain, the role for HO-2 is to produce CO which could then function as a messenger. However this has not yet been clearly defined. The function of CO produced by HO in tissues other than brain is also unclear, although CO can act as a smooth muscle relaxant (Wu and Wang, 2005). CO, like nitric oxide (NO), is considered a vasorelaxant via stimulation of cGMP. The vasodilator effect of CO in various vessels may be due to a CO-mediated decrease in the cytochrome P450-dependent generation of vasoconstrictors (Wu and Wang, 2005). Another important mechanism by which CO plays a major vasodilator role is through activation of the K_{Ca} channel (Wu and Wang, 2005; Li et al., 2008b). The biological actions of bilirubin may be especially relevant to the prevention of oxidant-mediated cell death (Wu and Wang, 2005). Bilirubin, at a low concentration, scavenges ROS in vitro, thereby reducing oxidant-mediated cellular damage and attenuating oxidant stress in vivo (Wu and Wang, 2005). In addition, biliverdin provides a defense against lethal endotoxemia and effectively abrogates the inflammatory response. HO-1-derived bilirubin has also been shown to display cytoprotective properties in the cardiovascular system (Wu and Wang, 2005; Hill-Kapturczak et al., 2002). Iron generated from the HO-1/HO-2 catalyzed degradation of heme is sequestered by ferritin induced by the release of iron. The increased iron concentration produced by increased HO activity is thought to cause increased expression of ferritin and ferritin synthesis, which serves to sequester iron, a potent cellular oxidant. Ferritin protects endothelial cells from oxidized LDL and iron-induced oxidative stress, and from ultraviolet (UV) light (Wu and Wang, 2005). Ferritin has also been shown to act as a cytoprotective antioxidant of endothelium (Wu and Wang, 2005), presumably due to anti-apoptotic effects (Wu and Wang, 2005). However it has been recently reported that heme is the only inducer of HO-1 that leads to increased synthesis of ferritin.

Recently, our group has shown that induction of HO-1 was associated with a parallel increase in the serum levels of adiponectin which has well documented anti-inflammatory properties (L'Abbate et al., 2007). Adiponectin has been ascribed antioxidative properties (Jung et al., 2006). The HO-1 mediated increase in adiponectin appears to provide the heart and vascular system with tolerance and resistance to oxidative stress generated not only in diabetes, but also to other types of vascular stress (Li et al., 2008b). These observations also serve to define some of the key mechanisms by which HO-1 is involved in diabetes and the metabolic syndrome. This review highlights the relationship between HO and hypertension and focuses on HO as a pivotal target enzyme in the development of hypertension therapy in the hypertensive animal models.

1.1. Heme oxygenase-1 and hypertension

The induction of HO-1 has been shown to lower blood pressure in several animal models. These are discussed below. No clinical studies in humans have been reported.

1.1.1. SHR model of hypertension—Blood pressure increases with age in young SHR, while adult SHR have an established hypertension (Wu and Wang, 2005; Sacerdoti et al., 1989). Overexpression of HO-1 normalizes blood pressure in young (8 weeks old) SHR to levels seen in normotensive control animals (Levere et al., 1990; Sacerdoti et al., 1989), but not in adult animals (20 weeks old) (Sacerdoti et al., 1989). In adult SHR, previous studies have demonstrated that both acute and chronic administration of an HO-1 inducer normalizes blood pressure. The normalization by 1-aminocyclopropanecarboxylic acid (ACPC) of blood pressure elevation and the reduced mortality to stroke was reported to involve induction of HO-1, resulting in antioxidant and vascular relaxation effects, in stroke-prone SHR (Gao et al., 2007). Heme administration decreased blood pressure in SHR (Abraham and Kappas, 2008; Levere et al., 1990; Botros et al., 2005). In contrast, treatment with HO inhibitors produced an increase in systemic arterial pressure (Wu and Wang, 2005; Li et al., 2007), even in normotensive rats, and magnified myogenic tone in gracilis muscle arterioles (Wu and Wang,

2005). HO-2 derived CO appears to be involved in the regulation of the basal vascular tone of resistant blood vessels (Wu and Wang, 2005). In blood vessels, CO produced from heme metabolism is reported to elicit relaxation (Kaide et al., 2001; Wu and Wang, 2005) through elevation of cGMP levels (Wu and Wang, 2005) and activation of potassium as well as other channels (Wu and Wang, 2005).

Furthermore, CO inhibits the activity of cytochrome P450 dependent reactions and thus the generation of vasoconstrictive substances, such as 20-HETE, ameliorating the development of hypertension (Omata et al., 1992) (Fig. 2). Therefore, it appears that the anti-hypertensive effect of HO activity enhancement may be due, in part, to blunting the vasoconstrictor action of 20-HETE (Abraham and Kappas, 2008). HO inhibitors decrease renal blood flow acutely, implying that the renal HO system supports renal circulation via formation of CO (Wu and Wang, 2005; Rodriguez et al., 2003).

A certain amount of confusion has arisen due to the diverse nature of the animal models used to study this phenomenon and which has been compounded by the use of metalloporphyrins to manipulate HO activity in these animal models. It has been suggested that HO-1 deficiency does not directly lead to the development of hypertension in mice (Wu and Wang, 2005). Moreover, treatment of normotensive rats with metalloporphyrins to inhibit HO activity resulted in an increase in systemic arterial pressure accompanied by an increase in peripheral resistance (Wu and Wang, 2005). This has led to the conclusion that a decrease in CO production as a result of the inhibition of HO activity was responsible since biliverdin and iron do not induce vasorelaxation (Wu and Wang, 2005). The daily injection (for 4 days) of a low dose of chromium mesoporphyrin (CrMP) increased the elevated blood pressure in 8-week-old SHR, while blood pressure in age-matched normotensive WKY rats remained unaffected (Wu and Wang, 2005). These demonstrate that different blood pressure responses to inhibition of HO activity in different strains of rats, reflect a strain-specific contribution of the HO/CO system to the regulation of blood pressure. A study in pregnant rats reported that increases in the HO-1/CO pathway inhibits soluble Flt-1 and soluble endoglin release, providing compelling evidence for a protective role of HO-1, and identifies HO-1 as a novel target for the treatment of preeclampsia, which is characterized clinically by hypertension and proteinuria (Cudmore et al., 2007). In contrast, cobalt cannot correct hypertension in an obese, diabetic SHR model (Ohtomo et al., 2008). Thus further study is required to elucidate the mechanism(s) that are involved in HO/CO system modification of blood pressure.

1.1.2. Angiotensin II—dependent hypertension/renovascular hypertension—

Angiotensin II is systematically and/or locally elevated in many forms of hypertension and is associated with increased vascular O_2^- production (Laursen et al., 1997; Raizada et al., 2000). Increased O_2^- has been shown to contribute to both the detrimental vascular and renal effects of angiotensin II. Previous studies have shown the induction of vascular, cardiac and renal HO-1 in response to angiotensin II in vitro and in vivo (Haugen et al., 2000; Ishizaka et al., 2000). HO-1 protein was increased in aortic adventitial and endothelial cells isolated from rats with angiotensin II-induced hypertension; however, treatment with losartan, a selective AT_1 -receptor antagonist, blocked the upregulation of HO-1 (Wu and Wang, 2005). Angiotensin II increases renal oxidant stress and HO activity caused by upregulation of HO-1 in renal proximal tubules (Haugen et al., 2000). In a rat model of radiation-induced nephropathy, the elevation of glomerular HO-1 protein levels was prevented by AT_1 -receptor antagonists, suggesting that angiotensin II mediates HO-1 induction (Wu and Wang, 2005). In contrast, treatment of rat VSMC with angiotensin II decreased HO-1 mRNA levels and this decrease was blocked by losartan (Wu and Wang, 2005). It is conceivable that angiotensin II-mediated upregulation of HO-1 is secondary to mechanisms that counteract the actions of angiotensin II.

An increase in the levels of the HO-1 gene may interrupt the vasoconstrictor pathway and attenuate the inflammatory aspect of the microcirculation in hypertension, i.e., oxidative stress, leukocytes/endothelial interaction and apoptosis (Wu and Wang, 2005), by increasing the levels of bilirubin and CO. Thus, the ability to upregulate HO-1 offers a unique therapeutic approach to the control of hypertension.

The products of the arachidonic acid metabolic pathway, mediated by the hemoproteins COX and cytochrome P450, have been reported, in animal models, to be responsible for hypertension. COX is considered a pro-inflammatory enzyme as free radicals and prostaglandin (PG)s are produced during its catalytic cycle. Although PGs are also involved in a variety of physiologic conditions including angiogenesis, hemostasis, or regulation of kidney function, upregulation of COX and increases in PGs levels are a common feature of inflammation (Abraham and Kappas, 2008). The results of our (Abraham and Kappas, 2008) and other groups studies (Suh et al., 2006; Kanu et al., 2006) show that HO-derived CO can inhibit COX activity. Also, HO activity has been implicated as a major regulator of several cytochrome P450s, including those responsible for the formation of 20-HETE. HO acts by limiting the amount of available heme and/or by producing CO, which binds strongly to the heme moiety of cytochrome P450, resulting in inhibition of cytochrome P450-mediated reactions (Abraham and Kappas, 2008). Such interactions may play an important role in the regulation of renal function. For example, selective induction of cortical and outer medullary HO-1 is associated with a decrease in 20-HETE, a potent vasoconstrictor, and normalizes blood pressure in SHR (Kaide et al., 2004; Abraham et al., 2002; Botros et al., 2002). It has been reported that renal medullary HO activity plays a crucial role in the control of pressure natriuresis and arterial blood pressure and that inhibition of the HO/CO system in the renal medulla may result in the development of hypertension in SD rats (Li et al., 2007). Hypoxia inducible factor (HIF)-1 α participates in the regulation of renal medullary function and long-term arterial blood pressure control via activation of oxygen-sensitive genes such as HO-1 and NOS in the renal medulla of salt-sensitive hypertensive SD rats (Li et al., 2008c). This suggests a critical role for HO-1 in the regulation of urine volume, electrolyte excretion and blood pressure (Abraham and Kappas, 2008).

Using cultured renal endothelial cells, erythropoietin-induced HO-1 expression was shown to provide cytoprotection against oxidative stress (Katavetin et al., 2007). In clipped and nonclipped kidneys from 2K1C hypertensive rats, induction of HO-1 and increased HO activity was reported as well as increased levels of the anti-apoptotic molecules Bcl-2 and Bcl-xL and decreased levels of the apoptotic molecules caspase 3 and caspase 9 (Botros et al., 2007). The induction of HO-1 has been shown to lower blood pressure and superoxide production of angiotensin in hypertensive mice (Vera et al., 2007). The induction of HO-1 also attenuated the development of hypertension and renal injury, leading to a decrease in angiotensin II-induced injury and salt-sensitive hypertension (Pradhan et al., 2006). Moreover, the induction of HO-1 prior to rapamycin treatment of transplant kidneys appears to limit the acute toxicity associated with rapamycin use (Goncalves et al., 2006). Upregulation of HO activity by gene transfer results in the normalization of blood pressure and increased expression of the anti-apoptotic molecules Bcl-2, Bcl-xL, AKT and pAKT in 2K1C renovascular hypertension (Olszanecki et al., 2007). This study further emphasized the anti-apoptotic action of the HO system as an important protective mechanism in kidney pathology. In contrast, induction of HO-1 by Tempol did not modify the mean arterial pressure in experimental renovascular hypertension of rats (Polizio et al., 2008). This difference remains to be resolved.

1.1.3. Pulmonary hypertension—Alterations occurring with the HO/CO system in pulmonary arteries in hypertension demonstrated that an impaired HO/CO-sGC/cGMP system in the pulmonary arteries of young and prehypertensive SHR was indicative of the pathogenesis and development of hypertension (Wu and Wang, 2005). It has been proposed that the

mechanism of pulmonary hypertension and pulmonary artery structural remodeling, induced by high pulmonary flow, is associated with changes in the endogenous CO/HO pathway (Li et al., 2006). Chronic hypoxia causes pulmonary hypertension with smooth muscle cell proliferation and matrix deposition in the wall of pulmonary arterioles. Hypoxia also induces a pronounced inflammation in the lung before the structural changes of the vessel wall occur. HO-1 transgenic mice are protected from the development of pulmonary inflammation, as well as hypertension, and vessel wall hypertrophy induced by hypoxia (Abraham and Kappas, 2008). These findings suggest a protective role for the enzymatic products of HO-1 catabolism in pulmonary hypertension (Ito et al., 2007).

In pulmonary arterial hypertension, IL-10 gene transfer significantly improved survival rates of monocrotaline-induced pulmonary hypertension, through the IL-10-mediated increase in HO-1 (Ito et al., 2007). Results from the European Community respiratory health survey in France show that, in heavy smokers, long HO-1 gene promoter (GT)_n repeats are associated with an increased susceptibility to develop lung dysfunction and airway obstruction (Guenegou et al., 2006).

1.1.4. Portal hypertension—The role of HO-1 in oxidative stress, inflammation, angiogenesis and splanchnic hemodynamics was examined in rats with portal hypertension (induced by partial portal vein ligation). Heme oxygenase was found to play an important beneficial role in attenuating oxidative stress and inflammation by regulating VEGF (Angermayr et al., 2006). A recombinant adenovirus carrying rat HO-1 (rAAV/HO-1) generated and injected through the portal vein resulted in a reduction in the severity of established micronodular cirrhosis (Tsui et al., 2005), which may help to decrease portal hypertension. Other reports have suggested a beneficial role for HO-1 overexpression in portal hypertensive rats (Abraham and Kappas, 2008).

2. Heme oxygenase, adiponectin and hypertension

In a recent series of studies we have reported that upregulation of HO-1 protein levels is associated with a concomitant increase in adiponectin expression (Abraham et al., 2008; Peterson et al., 2008; Li et al., 2008b; Kim et al., 2008; L'Abbate et al., 2007). Increased HO-1 protein levels have also been shown to lower blood pressure in several hypertensive animal models suggesting that adiponectin released from adipocyte enhances renal function. As a result, these studies were extended to examine the temporal relationship between HO-1 and adiponectin in hypertension.

Adiponectin is an adipose tissue-specific protein that has proved to have both antiatherogenic and insulin-sensitizing properties (Patel et al., 2007). Adiponectin exists as both low-molecular weight (LMW) oligomers and high-molecular weight (HMW) multimers (Berg et al., 2001; Basu et al., 2007). HMW adiponectin is reported to be more active and correlates with glucose and insulin levels when compared to LMW and total adiponectin (Basu et al., 2007; Kobayashi et al., 2004; Lara-Castro et al., 2006). Low plasma levels of HMW adiponectin have been consistently associated with obesity, insulin resistance, type 2 diabetes and coronary artery disease (Arita et al., 1999; Weyer et al., 2001). This review will focus in HMW adiponectin, the form that increases in parallel with the expression of HO-1 (L'Abbate et al., 2007; Abraham et al., 2008). Recently it was reported that hypoadiponectinemia is a predictor of the development of hypertension (Chow et al., 2007). However, the association between low adiponectin and the future occurrence of hypertension was independent of a homeostasis model assessment of insulin resistance (Chow et al., 2007), suggesting that hypoadiponectinemia might also influence blood pressure through other mechanisms that include endothelial dysfunction and the activation of the inflammatory cascade (Han et al., 2007). Moreover, adiponectin attenuates growth factor-induced proliferation of VSMC, which may lead to

hypertension through the development of vascular hypertrophy and stiffness (Mahmud and Feely, 2005).

Three studies have reported a negative association between plasma adiponectin level and blood pressure (Wang and Scherer, 2008; Iwashima et al., 2004; Adamczak et al., 2003). A study in young men showed that those with high-to-normal blood pressure have lower serum adiponectin levels (Wang and Scherer, 2008). Hypoadiponectinemia was shown to be a risk factor for hypertension after adjusting for age, body mass index BMI, and total cholesterol levels (Iwashima et al., 2004). A negative association between plasma adiponectin level and systolic blood pressure was significant only in obese subjects (Li et al., 2008a). Plasma adiponectin levels correlated with mean arterial pressure before adjusting for BMI, however, after adjusting for BMI, the relationship was not statistically significant (Adamczak et al., 2003). In contrast, the relationship between plasma adiponectin level and hypertension was independent of BMI (Iwashima et al., 2004; Wang and Scherer, 2008). Thus, in light of these contradictory results, the exact relationship between serum adiponectin levels and blood pressure, BMI, obesity and hypertension remains to be clarified.

In metabolic syndrome hypertension is a risk factor identified by the elevation of systolic and/or diastolic pressure. Similar to obesity, insulin resistance and dyslipidaemia, hypertension is associated with low levels of circulating adiponectin (Wang and Scherer, 2008; Adamczak et al., 2003; Iwashima et al., 2004; Kim et al., 2007; Della et al., 2005). Suppression of adiponectin levels may contribute to organ damage related to hypertension such as coronary artery disease, myocardial infarction, renal dysfunction and retinopathy (Hopkins et al., 2007; Kumada et al., 2003; Stenvinkel et al., 2004; Yilmaz et al., 2005). By contrast, adiponectin was elevated by treatment of hypertension with angiotensin-converting enzyme inhibitor (Furuhashi et al., 2003) and angiotensin II receptor blockers (Agata et al., 2004; Nomura et al., 2006). Angiotensin II infusion lowered adiponectin levels, whereas antioxidants blocked the angiotensin mediated decrease in adiponectin (Hattori et al., 2005).

Clinical studies show that low circulating adiponectin levels and hypertension correlated significantly with I164T polymorphism (exon 3) (Iwashima et al., 2004; Hopkins et al., 2007). T45G polymorphism (exon 2) correlated with coronary artery disease in diabetic subjects (Lacquemant et al., 2004). In addition, significant associations between G276T polymorphism (intron 2), increased adiponectin and decreased cardiovascular disease (CVD) risk were found in diabetic men (Qi et al., 2005). An increased prevalence of CVD and inflammation are present in end-stage renal disease (ESRD) patients. The -11377C/C polymorphism that occurs in this population was associated with a reduced CVD prevalence compared with the G/C genotype in ESRD patients (Stenvinkel et al., 2004).

The appearance of hypertension is associated with the development of atherosclerosis and a considerable body of research indicates that a low level of circulating adiponectin contributes to the development of atherosclerotic lesions (Ouchi et al., 2003, 1999; Hopkins et al., 2007). The role of insulin resistance in hypertension is unclear, however, insulin enhances vasodilation of human skeletal muscle vasculature through stimulation of endothelial NO production. Vasoconstriction occurs in insulin-resistant subjects, providing resistance to blood flow and giving rise to hypertension. Insulin resistance in the metabolic syndrome was directly correlated with the severity of hypertension, however, when measured by the insulin resistance index, insulin resistance only slightly increased the frequency of hypertension in the presence of all other metabolic syndrome risk factors (Hanley et al., 2002). The mechanism by which adiponectin levels are lowered in patients with hypertension remains to be clarified, although several mechanisms are worthy of consideration. First, activation of the renin-angiotensin system (RAS) occurs in adipose tissue as a result of hypoadiponectinemia, resulting in an increase in fat mass and blood pressure (Jones et al., 1997). RAS blockade in essential

hypertension increases adiponectin levels (Furuhashi et al., 2003). Second, inflammation contributes to the pathogenesis of hypertension. The insulin-sensitizing effect of exogenous adiponectin has been demonstrated in mice lacking endogenous adiponectin (Ruan and Lodish, 2004). Furthermore, these animals, when fed an atherogenic diet, developed obesity, insulin resistance, hyperglycemia, and hypertension (Ouchi et al., 2003). In humans, hypoadiponectinemia also precedes a reduction in whole-body insulin sensitivity (Stefan et al., 2002). Although it remains controversial whether insulin resistance can lead to hypertension, hyperinsulinemia, occurring in response to insulin resistance, has been shown to cause sympathetic activation in different tissues, including the kidney in rodents (Rahmouni et al., 2005, 2004). The emergence of hypertension in the absence of coexisting insulin resistance in adiponectin knockout mice maintained on a high-salt diet (Ohashi et al., 2006) suggests that hypoadiponectinemia also predisposes this animal model to hypertension via other pathways. Elevated free fatty acid levels in obese subjects appear to participate in obesity-related hypertension, via sympathoactivation (Rahmouni et al., 2005). Because adiponectin can reduce circulating fatty acid levels via enhanced fatty acid oxidation and reduced fatty acid synthesis (Xu et al., 2003), hypoadiponectinemia may increase the risk of hypertension in obese subjects through its adverse effects on fatty acid metabolism.

The mechanism by which HO-1 increases adiponectin levels is related to the function of HO-1 as a stress response/chaperone protein as well as its ability to decrease ROS by increasing glutathione and EC-SOD levels (Kruger et al., 2005; Abraham and Kappas, 2008; Turkseven et al., 2005) and by decreasing O_2^- production (Abraham et al., 2004; L'Abbate et al., 2007). PPAR agonists induce both HO-1 (Kronke et al., 2007) and the rate-limiting chaperone protein EroL (Ollinger et al., 2007; Wang et al., 2007). PPAR γ agonist which increases adiponectin may do so by increasing the levels of EroL chaperone protein (Ollinger et al., 2007). Since PPAR γ also increases HO-1 protein levels (Kronke et al., 2007) and HO-1 is known to be a chaperone protein, it is possible that one of the mechanisms by which HO-1 can increase adiponectin levels is through more efficient adiponectin stabilization and protection. This would confirm the report that the chaperone protein EroL increased adiponectin (Wang et al., 2007). We have reported that upregulation of HO-1 in diabetic rats provided both cardio- and vascular-protection against ROS (L'Abbate et al., 2007).

The seminal finding of decreased HO activity with a resultant decrease in CO generation in obesity suggests that CO may be involved as a signaling molecule in adiponectin secretion (Peterson et al., 2008). This is in contrast to a report that the metabolic syndrome increases endogenous CO production promoting hypertension and endothelial dysfunction in obese Zucker rats (Johnson et al., 2006). HO-derived CO was measured by Hb-CO but exhaled CO was determined by GC/MS. The difference in results remains to be elucidated, but could be explained by the use of different animal models and the high concentration of HO inhibitors used (Johnson et al., 2006).

The effect of HO-1 induction on the bone marrow fat cell is an indicator of the effect on adipogenesis. Heme oxygenase-1 induction decreased mesenchymal stem cell-derived adipocytes in bone marrow and may also decrease circulating adipocyte stem cells in the body. As a result, adipogenesis is decreased in bone marrow as well as in visceral and subcutaneous fat. This is associated with the loss of body weight even with normal food intake, an increase in adiponectin, insulin sensitivity and improvement in glucose tolerance (Peterson et al., 2008). The mechanism by which HO-1 increases insulin sensitivity may be related to HO-1 mediated reduction in IL-1 β , TNF α and IL-6 levels. Increased TNF α , IL-1 β and IL-6 expression resulted in an increase in insulin resistance in human obesity (Jager et al., 2007; Kern et al., 2001). Insulin acts centrally to decrease body weight, therefore the obesity state observed in obese (ob) mice is, in part, due to insulin resistance (Lazar, 2005). CoPP treatment decreased IL-1 β levels, improved insulin sensitivity and glucose tolerance (Peterson et al., 2008). The

HO-1-mediated increase in adiponectin modulates glucose tolerance and insulin sensitivity in mice. The HO-1-adiponectin regulatory axis ameliorates the deleterious effects of increased insulin resistance, obesity and the metabolic syndrome in critical areas of cell damage associated with cardiovascular disease and diabetes.

Adiponectin appears to have both beneficial and protective effects, including anti-inflammatory, vasculoprotective and anti-diabetic. Adiponectin may play a key regulatory and anti-inflammatory role in the development of hypertension (Fig. 3). Our recent demonstration that increased levels of HO-1 were accompanied by significant increases in adiponectin levels suggest the existence of a temporal HO-1-adiponectin relationship (Peterson et al., 2008; Li et al., 2008b; Kim et al., 2008). Therefore the upregulation of HO-1 accompanied by an increase in HO activity and the concomitant induction of adiponectin may play a central role in normalizing hypertension.

3. Summary

The demonstration that upregulation of HO-1 protein levels provides the heart and vascular system with tolerance and resistance to oxidative stress in diabetes and other forms of vascular disease is of clinical importance. The last decade has witnessed an explosion in the elucidation of the role of the HO system in human physiology. This system encompasses not only the heme degradative pathway, cytochrome P450, drug metabolism and renal function, but also the existence of an HO-1-adiponectin regulatory axis (Fig. 4). Their role in hypertension, portal and pulmonary hypertension are areas of intense research. This has focused not only on heme itself but also its metabolic products as well as endogenous compounds involved in a vast number of genetic and metabolic processes that are affected when heme metabolism is perturbed. The use of pharmacological agents (aspirin, statins, apolipoprotein A-I, heme arginate and metalloporphyrins) and genetic probes for manipulating HO has led to an examination of the complex relationship of the heme-HO system with biological and pathological systems. The strategy to target the HO-1-adiponectin axis as described in this review offers promising therapeutic approaches to clinicians for the effective management of hypertension. The approaches detailed within provide insights to the development of new therapeutic strategies against diseases that have, in the past, proved difficult to treat.

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Abbreviations

HO	heme oxygenase
CO	carbon monoxide
HO-1	heme oxygenase isozyme 1 (inducible form)
HO-2	heme oxygenase isozyme 2 (constitutive form)
ALA	δ -aminolevulinic acid

SnCl₂	stannous chloride
HETE	hydroxyeicosatetraenoic acid
COX	cyclooxygenase
CoPP	cobalt protoporphyrin IX dichloride
eNOS	endothelial nitric-oxide synthase
AKT	protein kinase (activator)
NO	nitric oxide
NOS	nitric oxide synthase
SHR	spontaneously hypertensive rats
K_{Ca} channel	large-conductance calcium-activated potassium channel
sGC	soluble guanylate cyclase
cGMP	cyclic guanosine monophosphate
ROS	reactive oxygen species
NF-κB	nuclear factor-κB
SNS	sympathetic nervous system
PG	prostaglandin
IL	interleukin
TNF	tumor necrosis factor
VSMC	vascular smooth muscle cell
L or D-4F	apolipoprotein, mimetic peptide

MAPK	mitogen-activated protein kinase
VEGF	vascular endothelial growth factor
ERK	extracellular signal-regulated kinase
AT1	angiotensin II type 1
Bcl-2	B-cell leukemia/lymphoma 2
Bcl-XL	B-cell leukemia/lymphoma extra long
JNK	Jun N-terminal kinase

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Fig. 1.

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. Heme oxygenase (HO), the rate-limiting enzyme in heme degradation exists in two isoforms, HO-1 (inducible) and HO-2 (constitutive).

Fig. 2.

The diagram illustrates the signaling pathways potentially affected by CO. CO activates soluble guanylyl cyclase (sGC), akin to its classical regulator NO, with the resultant increased production of cGMP. CO modulates mitogen-activated protein kinase activities (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, like NO, acts to stimulate cGMP, but also differs from NO. For example, CO produces vasodilation by inhibiting vasoconstrictors and activating K_{Ca} channels, ameliorates endothelial function, and is both anti-apoptotic and anti-inflammatory.

Fig. 3. Schematic representation of the role of adiponectin in blood pressure lowering. The anti-hypertensive effect of adiponectin involves a number of metabolic pathways that include the AMPK pathway, anti-inflammation, anti-proliferation and anti-sympathoactivation pathways. FFA, free fatty acid.

Effect of HO-1 and adiponectin on hypertension

Fig. 4.

Schematic representation of the potential mechanism of the anti-hypertensive properties of HO-1-adiponectin axis. Elevated levels of HO-1 and adiponectin are associated with lowered levels of blood pressure. CO, bilirubin and adiponectin combine in a symbiotic manner to achieve a decrease in hypertension.