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Forum Review

Protective Role of Heme Oxygenase-1 in Renal Ischemia

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ABSTRACT

Oxidative stress, which has been implicated in the pathogenesis of ischemic renal injury, degrades heme proteins, such as cytochrome P450, and causes the elevation in the level of cellular free heme, which can catalyze the formation of reactive oxygen species. Heme oxygenase-1 (HO-1), the rate-limiting enzyme in heme degradation, is induced not only by its substrate, heme, but also by oxidative stress. In various models of oxidative tissue injuries, the induction of HO-1 confers protection on tissues from further damages by removing the prooxidant heme, or by virtue of the antioxidative, antiinflammatory, and/or antiapoptotic actions of one or more of the three products, *i.e.,* carbon monoxide, biliverdin IXα, and iron by HO reaction. In contrast, the abrogation of HO-1 induction, or chemical inhibition of HO activity, abolishes its beneficial effect on the protection of tissues from oxidative damages. In this article, we review the protective role of HO-1 in renal ischemic injury, and its potential therapeutic applications. In addition, we summarize recent findings in the regulatory mechanism of *ho-1* gene expression. *Antioxid. Redox Signal.* 6, 867–877.

INTRODUCTION

Acute renal failure (ARF) is a syndrome associated with high mortality in humans, specially in the intensive care unit setting (42, 50). Current therapy is limited to supportive measures and preventive strategies, which fails to show definitive improvement in mortality (51, 82). Renal ischemia followed by reperfusion is known to result in significant renal epithelial cell injury (70), termed ischemic acute renal failure (IARF) (13). IARF, the major form of ARF, is often associated with sepsis in intensive care units (42). IARF injury is thought to be due to reactive oxygen species (ROS) generated by reperfusion (48, 66), which has been shown to be due, in part, to a rapidly increased free heme released from microsomal cytochrome P450 (CYP) (46, 65).

Heme oxygenase (HO) is the rate-limiting enzyme in the degradation of heme (104), which is catalyzed by a sequence of three enzymatic reactions, *i.e.,* NADPH-cytochrome P450 reductase, HO, and biliverdin reductase. HO converts heme to biliverdin IXα, carbon monoxide (CO), and iron (76, 90). Among the three HO isoforms reported, HO-1 is highly inducible by hemin and a vast array of other stimuli, including oxidative stresses (63, 76). In contrast, HO-2 and HO-3 are both expressed in constitutive fashion, and appear to function as heme binding molecules in normal cells (44, 49). The heme-derived metabolites were thought to be useless waste or toxic products; however, recent data suggest that the three products are not waste products, but useful metabolites that have significant biological properties, such as antioxidant, antiinflammatory, and/or antiapoptotic activities (15, 64, 83). The strong adaptive response of HO-1 to various stimuli suggests that HO-1 serves as a protective gene to confer resistance against inflammatory and oxidative tissue injuries, both of which are characteristics in the pathogenesis of ischemic renal injury.

HO-1 INDUCTION IN THE EXPERIMENTAL MODEL OF ARF

ARF is one of the best representative models of oxidative tissue injuries in which the roles of ROS and HO-1 can definitively be documented (4, 86). There are several experimental models of ARF, each with characteristic features.

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Glycerol-induced ARF

The glycerol-induced ARF in rats is the most commonly used model and is prepared by subcutaneous or intramuscular injection of hypertonic glycerol to animals (23). In this model, there are skeletal muscle injuries, termed "rhabdomyolysis," resulting in the release of myoglobin into plasma. Approximately one third of the patients with rhabdomyolysis are known to develop ARF (27), and rhabdomyolysis accounts for ~10% of all cases of ARF (27). A large amount of heme released from myoglobin may be directly responsible for the attendant lipid peroxidation that is associated with rhabdomyolysis (29).

Following the treatment with glycerol, HO-1 mRNA was found to increase >50-fold compared with that in untreated animals (57). The inhibition of increased HO activity by tin protoporphyrin (Sn-PP), a competitive inhibitor of HO activity (36), significantly aggravated the renal injury in this model. In contrast, induction of HO-1 by pretreatment of animals with hemoglobin resulted in the protection against ARF development (57). Thus, exposure of the kidney to an inordinate amount of hemoglobin elicited an adaptive cellular response that facilitates the clearance of cytotoxic free heme. These findings indicate that induction of HO-1, which itself is a free heme-catalyzed process, serves to clear an excess amount of free heme, ultimately resulting in a beneficial adaptive response. Moreover, treatment of rats with nephrotoxic serum prepared from sheep injected with a purified rat glomerular basement membrane extract, 24 h before the induction of glycerol-induced ARF, reduced functional and structural injury that occurs in this model (94). Of interest to note, HO-1 mRNA was induced in the kidney after the nephrotoxic serum administration, renal tubules were identified as the site of expression of HO protein, and inhibition of HO by Sn-PP prevented the protection afforded by nephrotoxic serum, suggesting that HO-1 is also a critical contributor in the acquired resistance (94).

Cisplatin-induced toxic renal injury

Cisplatin is a commonly used anticancer drug, but its use is often curtailed by its nephrotoxicity, particularly that on proximal tubules (71). However, by virtue of this unique effect, cisplatin has been utilized to prepare an experimental model of ARF. In contrast to the glycerol-induced ARF, iron derived from renal CYP is thought to be important in ROS formation in the cisplatin-induced ARF (7). In fact, it has been reported recently that CYP2E1-deficient mice show marked functional and histologic protection associated with the reduction of apoptotic cell death against cisplatin-induced renal injury. Incubation of the kidney slices in CYP2E1-deficient mice with cisplatin results in a significant decrease in the generation of ROS and attenuation of cytotoxicity as compared with that of the wild-type mice (43). HO-1 has been shown to be induced in a time- and dose-dependent fashion in the kidney following cisplatin administration. Administration of Sn-PP aggravated the renal injury (3), whereas preinduction of HO-1 by hemin treatment, or an overexpression of the *ho-1* gene by gene transfer, resulted in a significant amelioration of the cisplatin-induced renal injury (81).

IARF

The IARF injury is thought to be due, in part, to ROS generated by reperfusion (13, 66), which may also be the result of the rapid release of heme from microsomal CYP (46, 65). The reversibility of renal function in IARF critically depends on the length of the ischemic treatment prior to reperfusion, *e.g.,* longer than 60 min of ischemia resulting in an irreversible renal damage (22). There have been two types of IARF model: rats with bilateral ligation followed by reperfusion, and rats with a unilateral nephrectomy and the ligation of a contralateral renal artery. Maines *et al.* reported that renal HO-1 mRNA and its protein levels along with its enzyme activity were significantly increased after 30 min of bilateral renal ischemia followed by reperfusion in the rat (46). We also found that 40 min of renal ischemia in the uninephrectomized rat, which resulted in reversible IARF, significantly induced HO-1 mRNA and its enzyme activity (80). Inhibition of HO activity by tin mesoporphyrin (Sn-MP), a specific competitive inhibitor of HO (18), resulted both in a marked increase in intracellular heme content, and in the aggravation of renal function (Fig. 1). HO-1 induction thus plays an important role in the protection of renal dysfunction due to oxidative damages (80).

THE ROLE OF FREE HEME IN HO-1 INDUCTION AND TISSUE INJURY IN IARF

Heme is not only the substrate for HO-1, but also a strong inducer of HO-1 (76, 77). It is also involved in the repression of the nonspecific δ-aminolevulinate synthase (ALAS1), the rate-limiting enzyme in heme biosynthesis (25, 26, 34, 101). We determined the level of microsomal heme and the gene expression of ALAS1, in the kidney following ischemia/reperfusion. We found that, prior to HO-1 induction, there was a rapid and significant increase in microsomal heme concentration, which was followed by the inhibition of the gene expression of ALAS1 (80). These findings indicate that free heme concentration in the kidney is rapidly increased following ischemia/reperfusion, which may contribute to the induction of HO-1, as well as the repression of ALAS1, in the kidney. CYP represents the major heme source in the kidney because of its large content and rapid turnover (62, 72). It was also reported that ischemia/reperfusion of the kidney resulted in a significant decrease in the amount of microsomal CYP in rat kidney (46, 89). Although the nature of an increased microsomal heme in the kidney after reperfusion is not yet entirely clear, it is likely that microsomal CYP may be the source of "free heme." Thus, we speculate that ischemic renal cellular injury may destabilize heme from hemoproteins such as CYP, resulting in the induction of HO-1.

Although heme is required as the prosthetic group for heme proteins that are necessary for cellular viability (73), an excess amount of free heme is deleterious, because it would act as a prooxidant, leading to the generation of oxygen radicals (28). Free heme is also highly lipophilic and intercalates into the lipid bilayer of adjacent cells. Exposure of cells to heme is known to stimulate the expression of adhesion mole-

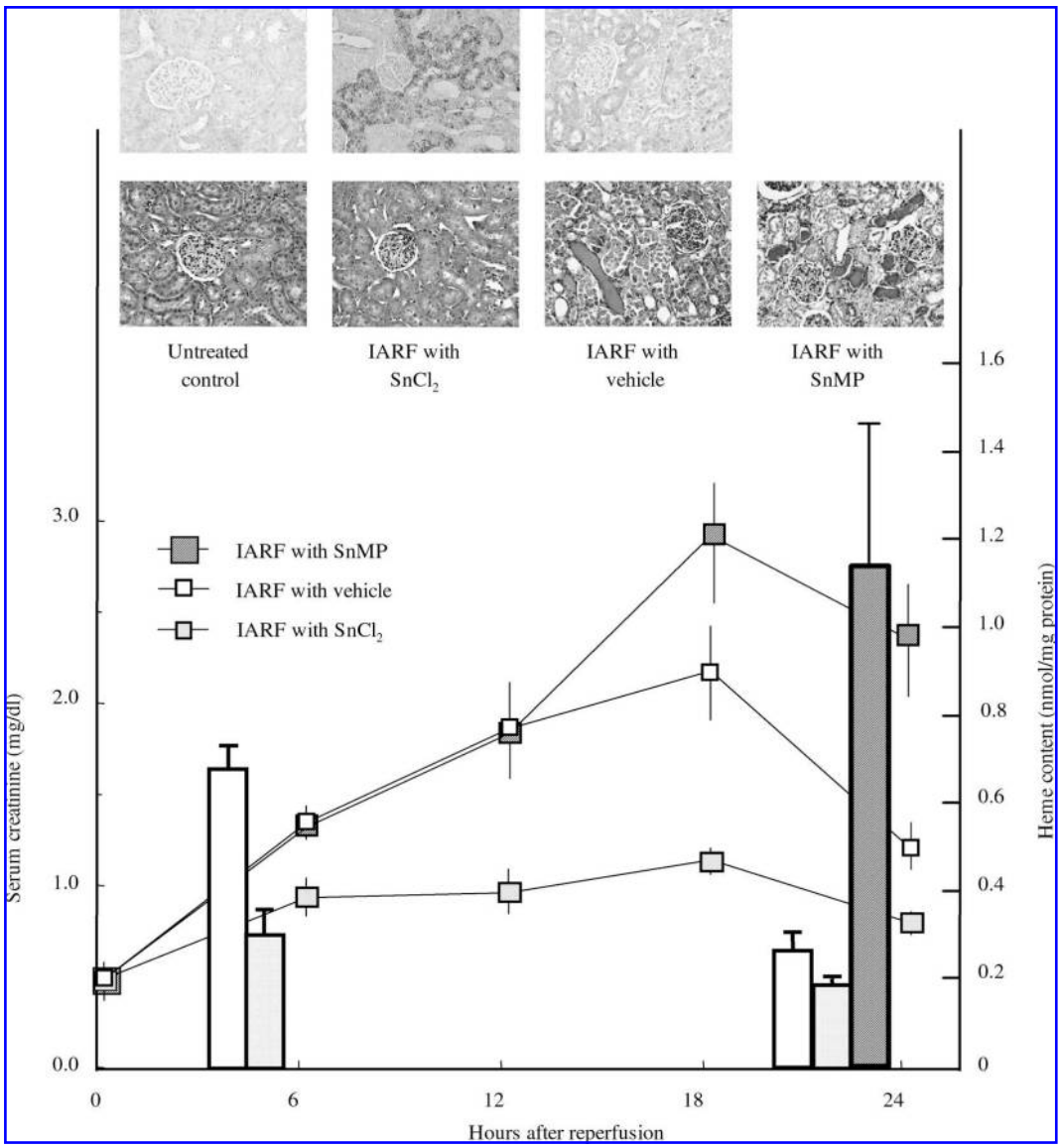

FIG. 1. Effect of $SnCl_2$ and Sn-MP administration on serum creatinine concentration, renal histopathology, and microsomal heme concentration in rats with IARF. Rats were uninephrectomized and subjected to unilateral ischemia for 40 min to produce IARF. $SnCl_2$ (10 mg/100 g of body weight) was administered subcutaneously, and Sn-MP (1 μmol/kg) was administered intravenously, at 24 h and 1 h prior to renal ischemia, respectively. After the initiation of reperfusion, whole blood was collected for the determination of serum creatinine concentrations, and kidney was removed for measurement of microsomal heme concentration and histological examination. $SnCl_2$ pretreatment ameliorated renal dysfunction with a decrease in microsomal heme concentration. In contrast, inhibition of HO activity by treatment with Sn-MP, which led to the accumulation of microsomal heme content, resulted in an aggravation of renal dysfunction. Columns indicate microsomal heme content. (**Insets**) *Top:* Kidney sections stained immunohistochemically, using anti-rat HO-1 as a primary antibody. After IARF, HO-1 protein was induced in tubular epithelial cells, while the induction became obvious in IARF with $SnCl_2$ pretreatment. *Bottom:* Kidney sections stained with hematoxylin and eosin. Extensive necrosis with cast formation in the proximal tubular cells was observed in IARF with vehicle treatment. It was aggravated in IARF with Sn-MP, in contrast to the relief from the injury in IARF with $SnCl_2$ pretreatment.

cules ICAM-1, VCAM-1, and E-selectin on endothelial cells *in vitro*, probably through heme-mediated generation of ROS, which underscores various reactive inflammatory changes (95). It has also been reported that heme, released from methemoglobin, catalyzes the oxidation of low-density lipoprotein, which in turn induces endothelial cytolysis caused by lipid hydroperoxides, suggesting its relevance to a variety of disorders, such as renal failure associated with intravascular hemolysis (35). We found that hemin treatment of intact rats significantly increased the DNA binding activity of nuclear factor-κB in a dose-dependent manner in the liver, which can lead to the activation of a proinflammatory cascade (55). We

also found that inhibition of HO activity by Sn-MP resulted in a marked increase in microsomal heme content, and in the aggravation of renal dysfunction in the IARF model (80). Thus, an enhanced and sustained increase in intracellular free heme concentration may aggravate the ischemic renal injury by accelerating the inflammatory process, and HO-1 induction plays an important role by removing the prooxidant, heme, in the protection of renal dysfunction.

HO-1 OVEREXPRESSION ALLEVIATES RENAL INJURY WITH IARF

Accumulating evidence overwhelmingly indicates that induction of HO-1 provides cytoprotective effects in various *in vitro* and *in vivo* models of the oxidative cellular injury (4, 63, 86). The importance of HO-1 in the protection against oxidant stresses is further documented in mice and humans that are deficient in HO-1 (69, 99). The adult HO-1-deficient mice developed an anemia associated with low serum iron levels, but increased serum ferritin levels. Nonheme iron accumulated in renal proximal cortical tubules, Kupffer cells, and hepatocytes. Such iron deposits contribute to oxidative damage by ROS production through the Fenton reaction and result in tissue injury and chronic inflammation. In fact, the extent of lipid peroxidation and protein carbonyls in the kidney of HO-1-deficient mice was significantly higher than that in control animals (68). It was also reported that the clipping of renal artery in HO-1-deficient mice led to an acute increase in ischemic renal damage and death (97). Moreover, adult HO-1-deficient mice were more vulnerable to death when challenged with endotoxin than control mice (69). The absence of HO-1 in a patient with hereditary HO-1 deficiency also accompanied an abnormally elevated serum heme concentration (~0.5 m*M*) and various oxidative, as well as inflammatory, complications (99). The HO-1-deficient patient also had persistent proteinuria and hematuria due to renal tubular injury (60). In contrast, overexpression of HO-1 by pharmacological intervention or by a gene transfer has been reported to prevent tissue injury in various models (1, 31). Maines and co-workers reported that a spin trap agent, *N-tert*-butyl-α-phenylnitrone, potentiated the induction of HO-1 at both transcriptional and protein levels in the kidney of IARF, which resulted in the decreased staining of iron and lipid peroxidation, suggesting that suprainduction of HO-1 protected the kidney from free radical-mediated injury (47). In contrast to warm ischemia in IARF, cold ischemic injury due to a long cold preservation time in kidney transplantation causes not only acute tubular necrosis, but also serious vascular endothelial cell injury (17, 103). Endothelial cells are vulnerable to oxidative stress in human HO-1 deficiency (99), and HO-1 overexpression in endothelial cells has been shown to confer protection against oxidative stress (2, 102). Recently, Tullius *et al.* reported that up-regulation of HO-1 in donor organs of the rat using cobalt protoporphyrin ameliorated ischemia/ reperfusion injury and improved the function of the grafted kidney for a long term (92). HO-1 overexpression in the donor kidney using a gene transfer approach also reduced the mortality and attenuated the ischemia/reperfusion injury in a rat renal isograft model (12).

Amelioration of IARF by tin chloride treatment

Tin chloride ($SnCl_2$) treatment is known to potently induce HO-1 in the kidney in a highly tissue-specific manner (37). We examined the effect of $SnCl_2$ treatment prior to ischemia/reperfusion and found that the treatment improved renal dysfunction, as shown by a marked decrease in serum creatinine concentration (Fig. 1). Whereas there was significant damage in proximal tubular cells in IARF control animals, there was hardly any damage in these cells in $SnCl_2$-pretreated animals (Fig. 1) (91). Following $SnCl_2$ treatment, a marked elevation of renal HO-1 mRNA was also observed, followed by increases in HO-1 protein expression and HO activity (91). HO-1 protein accumulated also specifically in the renal tubular epithelial cells following $SnCl_2$ treatment (Fig. 1). We also found that $SnCl_2$ treatment significantly attenuated the sustained increase in microsomal heme concentration after ischemia/reperfusion (Fig. 1). In contrast, inhibition of HO activity by the administration of Sn-MP, which led to the accumulation of microsomal heme, abolished the beneficial effect of $SnCl_2$ pretreatment on IARF, indicating the fundamental role of HO-1 activity by removing the prooxidant free heme, in the protection of renal epithelial cell injuries in IARF (Fig. 2) (91).

Very recently, it has been reported that $SnCl_2$ pretreatment is effective for the amelioration of the renal damage in another type of ARF. Chromium is commonly used in industrial chrome plating, welding, painting, metal finishes, steel man-

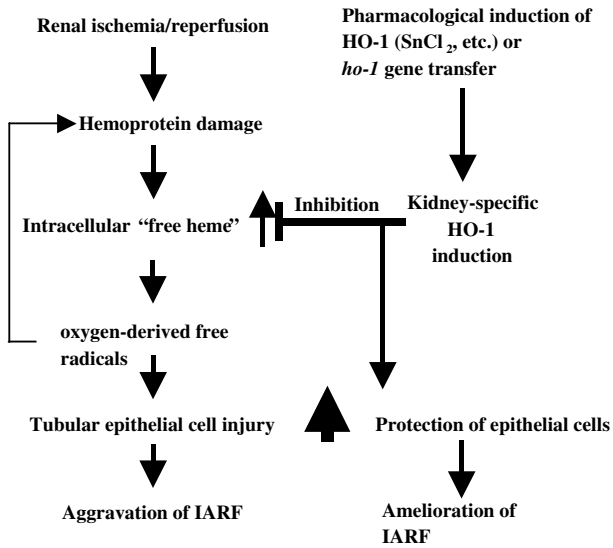

FIG. 2. Hypothetical sequence for the protection of renal epithelial cells by kidney-specific HO-1 induction. Renal ischemia/reperfusion destabilizes heme proteins, which results in an increase in intracellular "free heme" concentration. Kidney-specific HO-1 induction by pharmacological intervention, such as $SnCl_2$ treatment, or *ho-1* gene transfer degrades an excess amount of toxic free heme, leading to the amelioration of the ischemic renal injury.

ufacturing, alloy, cast iron, and wood treatment (9). Massive absorption of chromate is known to cause ARF in humans (96), and ARF induced by potassium dichromate ($K_2Cr_2O_7$) has been used as a model to study the pathophysiology of the disease. Experimental data show that chromate selectively damages the convoluted section of the proximal tubules (96), and ROS has been implicated in its pathogenesis (6). Barrera *et al.* reported that renal HO-1 overexpression induced by $SnCl_2$ is responsible for the attenuation of renal damage and oxidative stress in $K_2Cr_2O_7$-induced ARF of rats (11). They also showed that the protective effect of $SnCl_2$ is not associated with the induction of other antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase, suggesting that HO-1 induction is specific and indispensable in the protective effect of $SnCl_2$ on the $K_2Cr_2O_7$-induced ARF (10).

MECHANISM OF *ho-1* GENE REGULATION

HO-1 shows marked induction responses to treatment with hemin, as well as by a number of nonheme substances, such as insulin, epinephrine, endotoxin, heavy metals, hydrogen peroxide, ultraviolet, or sulfhydryl reagents (38, 45). The 5′-flanking region of both the human and the rat *ho-1* genes contains several potential *cis*-regulatory elements, such as cadmium-responsive element (Cd-RE), activator protein-1 (AP-1), interleukin-6-responsive element (IL6RE), and heat-shock element (HSE), which may facilitate gene transcription under stress (Fig. 3) (38, 53). Among them, Cd-RE, a 10-bp sequence, TGCTAGATTT, located at −4 kb, was shown to be necessary for the cadmium-mediated induction of the *ho-1* gene (88). On the other hand, Cd-RE is not apparently involved in *ho-1* gene activation by hemin, cobalt protoporphyrin IX, or sodium arsenite (88). AP-1, which is located immediately downstream of Cd-RE, is not involved in the cadmium-mediated induction of the human *ho-1* gene. On the other hand, AP-1 overlaps with Maf recognition element (MARE), an important domain that has a critical role in the *ho-1* gene transcription. HSE is the *cis*-acting element responsible for transcriptional activation of *heat shock protein* genes by heat shock. Heat shock treatment of rat cells, in fact, induces HO-1 at the transcriptional level (61, 78). In contrast to rat cells, however, HO activity in cultured cells derived from human, monkey, pig, and mouse is not necessarily induced by heat shock, suggesting that there may be interspecies difference in the heat-shock regulation of HO-1 expression (76). The proximal promoter region of the human *ho-1* gene also contains two copies of an IL6RE in normal orientation, and another in reverse orientation, and two functional CANNTG motifs, known as an E-box (52, 54, 74). Each IL6RE overlaps with the HSE or the E-box. Interleukin-6 (IL-6), an inducer of the acute-phase reaction, increases the expression of HO-1 and haptoglobin in human hepatoma cells (52). Thus, HO-1 is a positive acute-phase reactant in human hepatoma cells.

HO-1 induction responses in human cells appear to be also variable depending on the type of stresses used. It is generally thought that HO-1 is inducible by treatment with proinflammatory cytokines such as interferon-γ (IFN-γ), in both animal and human cells. For example, combined treatment with lipopolysaccharide (LPS) and IFN-γ in the human acute monocytic leukemia cell line, THP-1, induced *ho-1* gene expression (54), whereas IFN-γ treatment of the human glioblastoma T98G cell line suppressed it (85). Of note, Bach1, the heme-responsive transcriptional repressor of the *ho-1* gene, was induced by IFN-γ, whereas HO-1 expression was repressed by the same treatment in T98G cells (39).

As mentioned earlier, the AP-1 site also constitutes the MARE, or the nuclear factor erythroid 2 (NF-E2) site (30). NF-E2 is a heterodimer of an erythroid-specific subunit (p45) and a member of the Maf family of transcription factors (p18) (32). Recently, a transcription repressor Bach1 was identified as a mammalian heme-responsive transcription factor, and its repression activity on the *ho-1* gene was lost by heme binding, which in turn leads to transcriptional activation of the *ho-1* gene through the MAREs (59). Heme also up-regulates nuclear translocation of Nrf2, a partner molecule for the Maf family (14, 33), and promotes stabilization of Nrf2 (5). Thus, when intracellular heme concentration is increased, Bach1 is displaced from the MARE sequences by heme binding, which then allows binding of Nrf2 and other small Maf proteins, ultimately resulting in transcriptional activation of target genes that include *ho-1*, thioredoxin, and keratinocyte growth factor (Fig. 3) (14, 59). The MARE is also required for the hypoxic repression of the human *ho-1* gene expression (39). Thus, an appropriate control of the Maf/NF-E2 system by the switching on-off of Bach1 and Nrf2 binding to the MARE sequence appears to be critical for normal cellular functions. For example, it is known that its deregulation leads to tumorigenesis (16). Therefore, various repressors and activators, such as Bach1 and Nrf2, respectively, may be importantly involved in the transcriptional control of the *ho-1* gene. The fact that the DNA binding activity of Bach1 is regulated by heme suggests that the stability of the gene expression program by Bach1 is directly influenced by intracellular heme concentrations. It should be noted that Bach1 knockout mice showed also significant *ho-1* gene activation, suggesting that low-level HO-1 expression in the wild-type mice under normal physiological conditions is due to repression by Bach1, rather than a lack of activation (84). Thus, the Bach1–*ho-1* system is the first example in higher eukaryotes that involves a direct regulation of a transcription factor for an enzyme gene by its substrate (84).

Regulation of *ho-1* gene expression by hypoxia is also species-specific. For example, hypoxia treatment of cultured cells from rat (20), mouse (98), bovine (39), and monkey cells (39) induced *ho-1* gene activation, whereas many human cells studied in culture, with one exception of human dermal fibroblasts (67), showed suppression of gene expression (39, 56). Similar to rat cell cultures, HO-1 is also inducible in the rat brain *in vivo* following transient forebrain ischemia (87). During hypoxia, the level of hypoxia-inducible factor (HIF)-1α increases because its normal degradation is suppressed by hydroxylation of a specific proline residue in its oxygen-dependent prolyl hydroxylase domain (PHD) (75). The *ho-1* gene contains an HIF-binding site (40), although the functional significance of HIF in the induction of HO-1 in

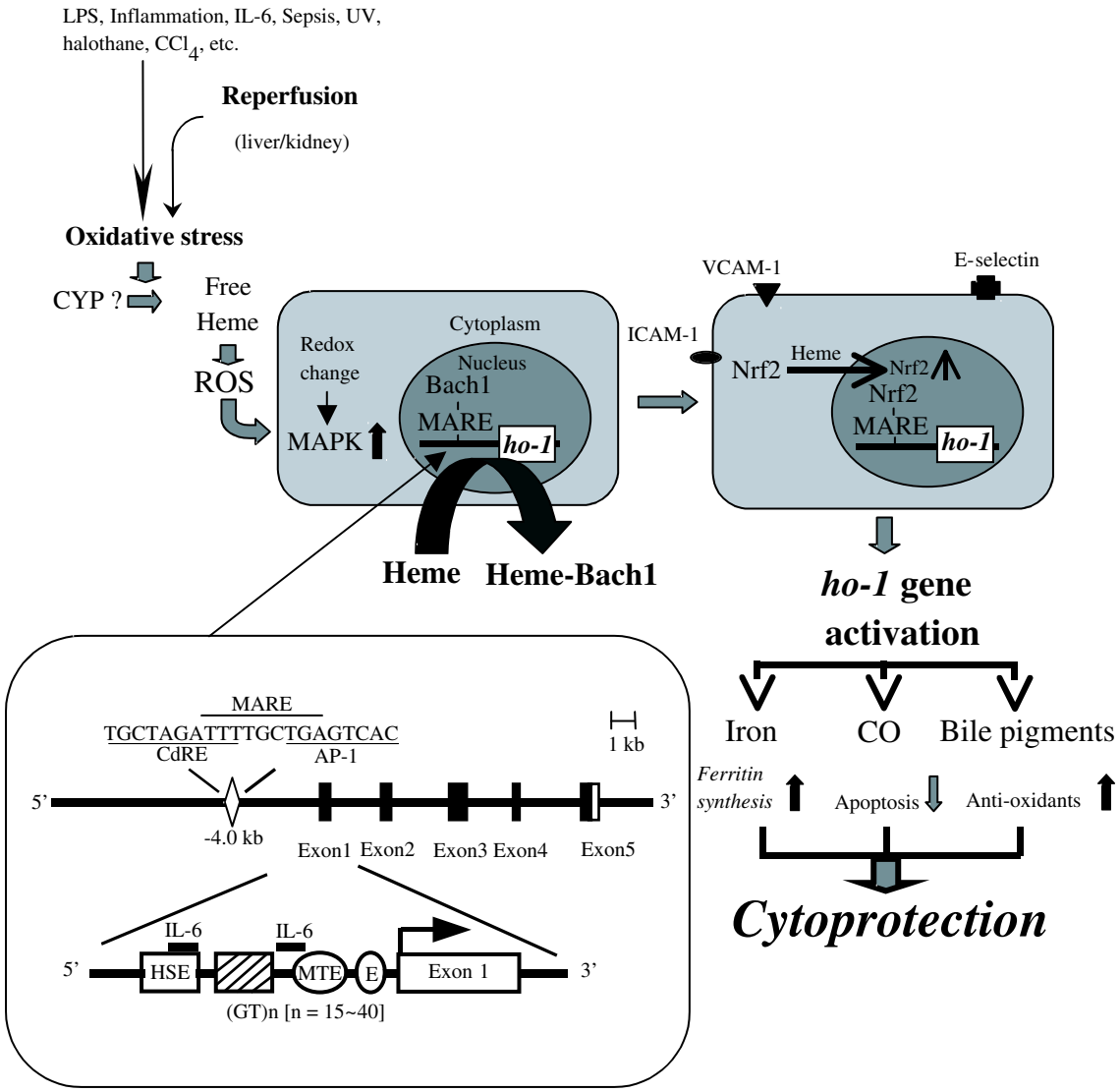

FIG. 3. Hypothetical mechanism of *ho-1* gene regulation. Hypothetical mechanism of *ho-1* gene regulation by oxidative stress is shown, based largely on findings in the liver, lung, and kidney cells, but the concept may apply widely. Various oxidative stresses, such as LPS, inflammation, IL-6, sepsis, UV, halothane, CCl_4, IARF, and multiple organ dysfunction syndrome, result in the production of free heme, most likely released from CYP. Free heme is then involved in the generation of ROS, which result in a change in the redox state in the cell, and in the activation of the MAPK signaling pathway. Free heme also binds with Bach1, the transcriptional repressor of *ho-1*, and permits its detachment from MARE sequence in the *ho-1* promoter. This in turn allows Nrf2 binding with MARE, and results in the transcriptional activation of the *ho-1* gene. Heme is also known to stimulate nuclear translocation of Nrf2. Increased HO-1 activity metabolizes free heme to iron, CO, and biliverdin IXα. Iron is directly sequestered and inactivated by coinduced ferritin. CO suppresses apoptosis of endothelial cells via the activation of p38 MAPK. Biliverdin IXα is rapidly converted to bilirubin IXα by biliverdin reductase and serves as a major antioxidant. Thus, all these metabolites of the HO reaction act as members of the adaptive response and confer protection to cells against oxidative injuries. (**Insets**) The composite enhancer and the proximal *cis*-acting elements of the *ho-1* gene are schematically shown. Also shown is the polymorphic $(GT)_n$ repeat in the *ho-1* promoter. Human *ho-1* gene contains a potential HSE, although it appears to be silent in most human cells. It also contains two IL6REs in normal orientation, and another in reverse orientation, and it is known that IL-6 treatment induces *ho-1* gene expression. The upstream *cis*-acting element of the human *ho-1* gene, located at −4 kb, consists of the Cd-RE and an AP-1 binding site. The AP-1 site also constitutes the MARE sequence, the key *cis*-regulatory sequence of the *ho-1* gene. A transcriptional repressor, Bach1, binds with MARE, to keep the *ho-1* gene repressed in normal cells. Its repression is released when Bach1 binds with heme.

response to hypoxia remains elusive. These equivocal findings appear to be due, in part, to different species used in the study. Recently, it was shown in mouse cardiomyocyte cultures that activation of the PHD oxygen-sensing mechanism increased by metabolic inhibition, which also accompanied the induction of HO-1 (98). This finding suggests that hypoxia may induce HO-1 via the PHD oxygen sensor as the mediator (98).

In addition, a $(GT)_n$ dinucleotide repeat in the 5′-flanking region of human *ho-1* gene shows length polymorphism and could modulate the level of gene transcription (Fig. 3). The long $(GT)_n$ repeat in the *ho-1* gene promoter appears to reduce HO-1 inducibility by ROS, such as those in cigarette smokers, and contribute to the development of chronic pulmonary emphysema (100). In contrast, the small size of a $(GT)_n$ allele was found to be associated with a reduced incidence of emphysema. Short repeat $(GT)_n$ alleles were also associated with reduced postdilation restenosis following balloon dilation in percutaneous transluminal angioplasty (19), suggesting that up-regulation of the *ho-1* gene may be an important protective factor against emphysema or restenosis. However, longer $(GT)_n$ repeats may also have an advantage in certain conditions, such as cerebral malaria, a severe complication of malarial infection (79). In this case, it appears that lower HO-1 expression in the longer $(GT)_n$ repeats may be adapted to decrease intracellular concentration of iron, thereby providing protection against the development of cerebral malaria. Cerebral malaria appears to be an exception to the rule. It may be due, in part, to the following: (a) several genes are known to have been selected as the protective factor against malaria over the long history of human diseases; (b) malarial infection might be especially significant in the selection of HO-1 as a protective gene because of intensive production of hemozoin throughout one's life; and (c) cerebral malaria is one of the most deadly diseases known to date.

METABOLIC CONSEQUENCES OF HO-1 INDUCTION

The immediate and adaptive response of HO-1 specific to the wide variety of oxidative injuries clearly suggests an important role of HO-1 in the protection of oxidative stresses, in addition to its key role in heme catabolism. The absence of HO-1 is associated with an abnormally elevated serum heme concentration and results in various oxidative and inflammatory complications (69, 99), indicating the fundamental role of HO-1 in the protective response.

Free heme can be liberated from heme proteins under oxidative conditions (55, 58, 80). Heme is known to activate endothelial cells and promote proinflammatory gene expression probably mediated through heme-dependent ROS generation (95). HO breaks down the prooxidant heme into three elements, *i.e.,* iron, biliverdin IXα, and CO (Fig. 3). Iron, which is an oxidant, is directly sequestered and inactivated in the cell by coinduced ferritin (93). HO-1 has been reported also to prevent cell death by exporting intracellular iron *in vivo* (68) and *in vitro* (21). Biliverdin IXα is rapidly converted by biliverdin reductase to bilirubin IXα. Both biliverdin IXα and bilirubin IXα, as well as their glucuronides, are potent antioxidants (83). The recent description of redox cycling in which biliverdin is converted to bilirubin by biliverdin reductase, with bilirubin being recycled back to biliverdin, suggests a mechanism that would amplify the antioxidant effects of these bile pigments (8). CO produced from heme by HO can also suppress apoptosis of endothelial cells via the activation of p38 mitogen-activated protein kinase (MAPK) (15). CO at low concentrations also differentially and selectively inhibited the LPS-induced expression of proinflammatory cytokines and increased the expression of the antiinflammatory cytokine via p38 MAPK (64). Recently, it was also reported that the ability of an antiinflammatory cytokine interleukin-10 (IL-10) to suppress tumor necrosis factor-α expression in macrophages requires the presence of HO-1 and the generation of CO. In this model, HO-1 expression and CO administration had comparable effects as those of IL-10 (41). The protective effect of IL-10 in the lethal endotoxic shock model in mice was also strictly dependent on HO-1 expression and CO production (41). HO-1-deficient mice also exhibit lethal ischemic lung injury, but can be rescued from death by CO inhalation. In this model, CO exerted ischemic protection by activating soluble guanylate cyclase and thereby suppressed hypoxic induction of the gene encoding plasminogen activator inhibitor-1 (PAI-1) in mononuclear phagocytes. As a result, accrual of microvascular fibrin was suppressed, and CO-mediated ischemic protection observed in the wild-type mice was not observed in mice null for the PAI-1 gene expression, suggesting a critical link between CO and prevention of ischemic injury (24). Thus, in addition to the removal of the prooxidant heme, all these metabolites of the HO reaction constitute the protective response axis, and serve against oxidative stimuli, by additional mechanisms (Fig. 3).

CONCLUSION

In this review, recent evidence concerning the protective role of HO-1 in oxidative tissue injury was summarized with particular focus on the ischemic renal injury. Both inhibition of HO activity and suppression of *ho-1* gene expression led to marked aggravation of the ischemic renal injury. In contrast, induction of HO-1 by gene transfer, or by pharmacological induction, conferred significant protection against the ischemic renal injury at least in part removing the prooxidant free heme. The three metabolites of heme by HO reaction also contribute to the protection of cells from oxidative damage. These findings suggest that HO-1 may play a critical role in the defense against the ischemic renal injury. Tissue-specific HO-1 expression in the kidney, such as by HO-1 gene transfer, or by treatment with $SnCl_2$, which specifically induces kidney HO-1, may provide a new therapeutic modality for the ischemic renal injury.

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ABBREVIATIONS

ALAS1, nonspecific δ-aminolevulinate synthase; AP-1, activator protein-1; ARF, acute renal failure; Cd-RE,

cadmium-responsive element; CO, carbon monoxide; CYP, cytochrome P450; HIF, hypoxia-inducible factor; HO, heme oxygenase; HSE, heat-shock element; IARF, ischemic acute renal failure; IFN-γ, interferon-γ; IL, interleukin; IL6RE, interleukin-6-responsive element; $K_2Cr_2O_7$, potassium dichromate; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MARE, Maf recognition element; NF-E2, nuclear factor erythroid 2; PAI-1, plasminogen activator inhibitor-1; PHD, prolyl hydroxylase domain; ROS, reactive oxygen species; $SnCl_2$, tin chloride; Sn-MP, tin mesoporphyrin; Sn-PP, tin protoporphyrin.

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