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Forum Review

Heme Oxygenase-1: Redox Regulation and Role in the Hepatic Response to Oxidative Stress

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ABSTRACT

Heme oxygenase (HO) catalyzes the oxidative cleavage of the α-mesocarbon of Fe-protoporphyrin-IX yielding equimolar amounts of biliverdin-IXα, free divalent iron, and carbon monoxide (CO). Among the three isoenzymes cloned to date, only HO-1 can be induced by a variety of seemingly disparate stimuli, most of which are linked by their ability to provoke oxidative stress. Although constitutive expression of HO-1 in the liver is restricted to Kupffer cells, the gene is inducible in nonparenchymal as well as in parenchymal liver cells. HO-1 induction potentially confers protection against oxidative stress in a variety of experimental models, such as liver ischemia/reperfusion secondary to transplantation or hemorrhage/resuscitation. Induction of HO-1 may protect the cell against oxidative injury by (a) controlling intracellular levels of "free" heme (a prooxidant), (b) producing biliverdin (an antioxidant), (c) improving nutritive perfusion via CO release, and (d) fostering the synthesis of the Fe-binding protein ferritin. Although protective effects of up-regulation of the HO pathway—presumably through production of bile pigments and CO—have been reported for a variety of cells and tissues, including the liver, evidence suggests that the protective action might be restricted to a rather narrow threshold of overexpression. High levels of HO-1 may even sensitize the cell to oxidative stress, *e.g.*, through release of reactive iron. Transcriptional activation of the HO-1 gene is an integral part of the cellular response to oxidative stress, but its induction seems to be neither exclusively cytoprotective nor exclusively cytotoxic. *Antioxid. Redox Signal.* 4: 749–758.

HEME, HEME OXYGENASE (HO), AND HO ISOZYMES

HEME is a ubiquitous molecule containing an active iron center that carries a high affinity for molecular oxygen and can donate electrons. The high affinity for oxygen allows for reversible binding, transport, and storage of oxygen in hemoglobins and myoglobin. Furthermore, by virtue of its cardinal function as an electron donor in repetitive oxidation/reduction cycles, the heme prosthetic moiety is of outstanding significance for electron transfer: Heme groups serve as the catalytic site and act tightly bound to a variety of proteins involved in aerobic metabolism, including respiratory chain cytochromes and numerous synthetic and degradative cytochrome P450 isoenzymes (43). "Free" cellular heme may derive from these ubiquitous heme proteins and may act as a prooxidant (3, 20). Thus, free heme is potentially toxic and intracellular levels are vanishingly small in most cells. Hepatocytes contain a small but critical pool of regulatory heme, which is indicative of the cell's actual heme requirements (9, 18, 19). The concentration of free cellular heme is tightly controlled by the fine balance of synthesis and degradation of the molecule: Whereas regulation of hepatic heme biosynthesis is accomplished through the modulation of δ-aminolevulinic acid synthase (ALA synthase; EC 2.3.1.37) activity (50), the enzymatic degradation of heme is controlled predominantly by microsomal HO (EC 1.14.99.3) isoenzymes that catalyze the initial and rate-limiting step in heme catabolism (83). Oxidative cleavage of the α-mesocarbon bridge of b-type heme molecules by HO yields equimolar quantities of biliverdin-IXα and carbon monoxide (CO), while the central iron is released. Nonenzymatic pathways of heme degradation also exist, but

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are of limited significance (7). Both ALA synthase and HO are regulated by the cellular heme content (13).

Dysregulation of the critical balance of heme biosynthesis and degradation under pathophysiological conditions may result either in accumulation of toxic porphyrins (as in the case of hepatic porphyrias) or in impaired availability of heme prosthetic moieties for biosynthesis of hemoproteins. Consistent with the latter concept, administration of interleukin-1β induced an increase in hepatic HO activity along with a decrease in ALA synthase activity in the rat liver, and the resulting decrease in the cellular heme pool was reflected in an impairment of cytochrome P450 synthesis and availability (33).

In most mammalian species, biliverdin-IXα is subject to further degradation to bilirubin, which occurs through the action of the cytosolic enzyme biliverdin reductase (34). In addition, biliverdin may form complexes with concomitantly released iron ions (97, 98). The cellular fate of CO formed during heme degradation is only incompletely understood. CO may bind to oxyhemoglobin, as well as to other heme-containing proteins, thereby presumably affecting their heme prosthetic moieties and activity as has been previously reported for nitric oxide (NO) (44, 80). With respect to the liver, CO effects seem to include activation of soluble guanylate cyclase (sGC) in hepatic stellate cells (79), which are sinusoidal pericytes controlling sinusoidal tone and blood flow distribution (57, 99), as well as effects on contractility of bile canaliculi (74). Ultimately, CO is exhaled by the lungs, and gas chromatographic analysis of exhaled CO can serve to assess HO activity *in vivo* (90), because CO and biliverdin are formed in equimolar amounts during heme degradation.

The enzyme systems regulating heme synthesis and degradation are not evenly distributed among organs and tissues, and HO activity is particularly high in spleen, testes, brain, and liver (42). In addition, the liver is the second most active heme-producing tissue. All isozymes, *i.e.,* HO-1, -2, and -3, cloned (10, 51, 71, 73) and described to date are expressed in the liver (45, 51). HO-3, which has been cloned recently, has a substantially lower catalytic activity than the isozymes 1 and 2. Although functions and regulation of HO-3 are incompletely understood, there is evidence to suggest a role in binding or transporting heme within the cell (51). Although HO-1 and HO-2 catalyze the same reaction and have similar cofactor requirements (NADPH, O_2, NADPH cytochrome P450 reductase), they substantially differ with respect to regulation and expression pattern in various tissues, including the liver. They are encoded by distinct genes located on chromosomes 22q12 (HO-1) and 16q13.3 (HO-2) in the human genome (35, 36). HO-1 and –2 proteins differ in molecular weight and are immunologically distinct (86). c-DNA probes and antibodies that are specific for these two isoenzymes have been used to characterize the organ-specific expression pattern: Whereas HO-2 message and immunoreactive protein are particularly abundant in the normal liver, only faint amounts of HO-1 transcripts and protein can be found under physiological conditions (4, 14). Little is known about the regulation of HO-2. This isoenzyme—also referred to as the "constitutive" isozyme—does not seem to be inducible by oxidative stress in the liver (4). Although the promoter of the HO-2 gene contains a glucocorticoid response element, which seems to be functional in neuronal tissue of postnatal rats (46), dexamethasone failed to increase HO-2 mRNA and protein in adult rats in the liver (own unpublished observation). In any case, the substantial increase in hepatic HO activity observed in the "induced" liver is likely mediated by the up-regulation of HO-1, mainly by increase in gene transcription rates (4, 75). HO-1 has been identified as the major 32-kDa heat shock (stress) protein hsp32 (72). Its regulation as part of the hepatic response to oxidative stress will be discussed in detail later in this review.

DISTRIBUTION OF ISOZYMES IN THE NORMAL LIVER: A TOPOGRAPHIC BASIS FOR UNDERSTANDING THE DIFFERENT ROLES OF HO ISOFORMS

The liver plays a significant role in removal of both damaged red cells and free hemoglobin from the circulation. Early work by Bissell and coworkers demonstrated a discriminate role for parenchymal and sinusoidal cells in the catabolism of hemoglobin and senescent red cells (8). We (4) and others (16) have demonstrated that the cooperative role of parenchymal and nonparenchymal cells in heme catabolism is reflected in a discriminate expression pattern of the isoenzymes HO-1 and -2 in hepatocytes and sinusoidal cells in the normal liver. The high HO activity associated with hepatocytes can be attributed almost exclusively to HO-2. In contrast, a functional basal expression of the HO-1 gene is observed in Kupffer cells, the liver-specific tissue-fixed macrophages. This basal expression seems to be required for physiological iron reutilization because isolated destruction of the HO-1 gene results in anemia with abnormally low serum iron levels despite a functional HO-2 gene (58).

The compartmentalization of the isoenzymes seems to be of outstanding functional significance for the actions of CO. CO, a long disregarded by-product of the pathway, can avidly bind to ferroheme compounds, most notably oxyhemoglobin. Thus, CO produced by hepatocytes may readily reach hepatic pericytes or stellate cells located on the abluminal surface of endothelial cells in the space of Disse (91), thereby regulating sinusoidal blood flow in a paracrine manner (16). In addition, autocrine production of CO by hepatic stellate cells may also be of functional significance (79). In contrast, release of CO into the sinusoid by cells located within the sinusoid, such as Kupffer cells, or release of CO directed to the luminal surface of endothelial cells is likely to be quenched by abundantly available ferroheme groups from hemoglobins (16). Consistent with this concept, the pressor effect of false substrates of the HO pathway, such as zinc protoporphyrin-IX (ZnPP-IX) or tin protoporphyrin-IX (SnPP-IX), is more profound in the isolated liver perfused in the absence of red blood cells with Krebs–Henseleit buffer as compared with *in vivo* preparations (6, 79).

HO-1 AND HEPATIC OXIDATIVE STRESS RESPONSE

HO-1 is highly inducible by a variety of discriminate stimuli inducing hepatic oxidative stress in parenchymal and nonparenchymal cellular compartments and modulates the liver

response to these stress events (Fig. 1). Previous work on regulation of the expression of HO isoenzymes indicates that up-regulation of HO activity under stress conditions primarily reflects induced HO-1 gene expression involving two fundamental regulatory pathways. The different inducers of HO-1 act either via a heme-dependent (heme, the heme precursor ALA, phenobarbital) or a heme-independent (*e.g.,* transition metals, heat shock) mechanism. Despite the differences, the effects of the diverse factors on hepatic HO-1 gene expression appear to be controlled mainly at the transcriptional level (4, 75). Thus, the broad spectrum of inducing agents essentially reflects the presence of a variety of transcriptional enhancer elements, including binding sites for activator protein-1 (AP-1) and nuclear factor κB (NFκB) as well as hypoxia response, cadmium response, heat shock response, metal response, and interleukin-6 response elements within the HO-1 promoter (for review, see 13). In contrast, the HO-2 gene contains only a single glucocorticoid response element in the 5′ flanking region, which seems however to be functional *in vivo* and *in vitro* (17, 46, 60).

Although regulation of HO-1 gene expression in the intact liver is incompletely understood, evidence would suggest that the so-called redox-sensitive transcription factors NFκB and AP-1 play a significant role in regulation of the HO-1 gene under conditions associated with oxidative stress. Studies using primary chick embryo liver cells transiently transfected with reporter gene fusion constructs revealed a role for the activation of the AP-1 element in HO-1 induction by sodium arsenite and cobalt chloride ($CoCl_2$) (41). Similarly, correlational evidence would suggest that enhanced oxidative stress during aging is accompanied by a compensatory induction of the antioxidant enzyme HO-1 through reactive oxygen species (ROS)-dependent activation of the NFκB pathway in hepatocytes (39). HO-1 induction by the substrate heme seems to be regulated by activation of NFκB and AP-2 *in vitro* (38). NO, another radical species, may induce HO-1 gene expression in hepatocytes mediated via the protein kinase G pathway and a cyclic AMP response element/AP-1 element (24). Thus, the redox-sensitive transcription factors AP-1 and NFκB might contribute to transcriptional activation of the HO-1 gene under appropriate conditions. Consistent with the aforementioned *in vitro* data, results from our laboratory suggest that HO-1 induction in the liver after hemorrhage and resuscitation results from a ROS-dependent activation of AP-1 because the antioxidants tempol or trolox attenuated both AP-1 activation and HO-1 accumulation. In addition, HO-1 gene expression was inhibitable by dexamethasone (65). Similarly, data obtained by Oguro *et al.* are consistent with a regulatory role of AP-1 binding for HO-1 induction in a model of glutathione depletion by phorone in the intact rat liver (52).

There is substantial evidence to suggest that formation of ROS in the intact liver *in vivo* is subject to compartmentalization, which results in cell type-specific and acinar heterogeneity of the oxidative stress response (27–29). Thus, regulation of redox-sensitive genes, such as HO-1, by ROS should occur within different compartments depending on the site and nature of the stress event. Consistent with this concept, a highly localized induction of HO-1 immunoreactive protein was observed after different oxidative stress events, including endotoxemia, glutathione depletion, and $CoCl_2$ challenge with marked acinar and cell type-specific heterogeneity of HO-1 expression (4). Although lipopolysaccharide (LPS) induced a marked activation of NFκB and induced the HO-1 gene in Kupffer cells, it failed to up-regulate HO-1 gene expression in hepatocytes. Conversely, glutathione depletion with phorone and buthionine sulfoximine or $CoCl_2$ challenge led to a substantial induction of HO-1 gene expression in hepatocytes without affecting nonparenchymal cells. Although $CoCl_2$ challenge and glutathione depletion both induced HO-1 exclusively in hepatocytes, the acinar expression was markedly different: Whereas glutathione depletion induced HO-1 gene expression

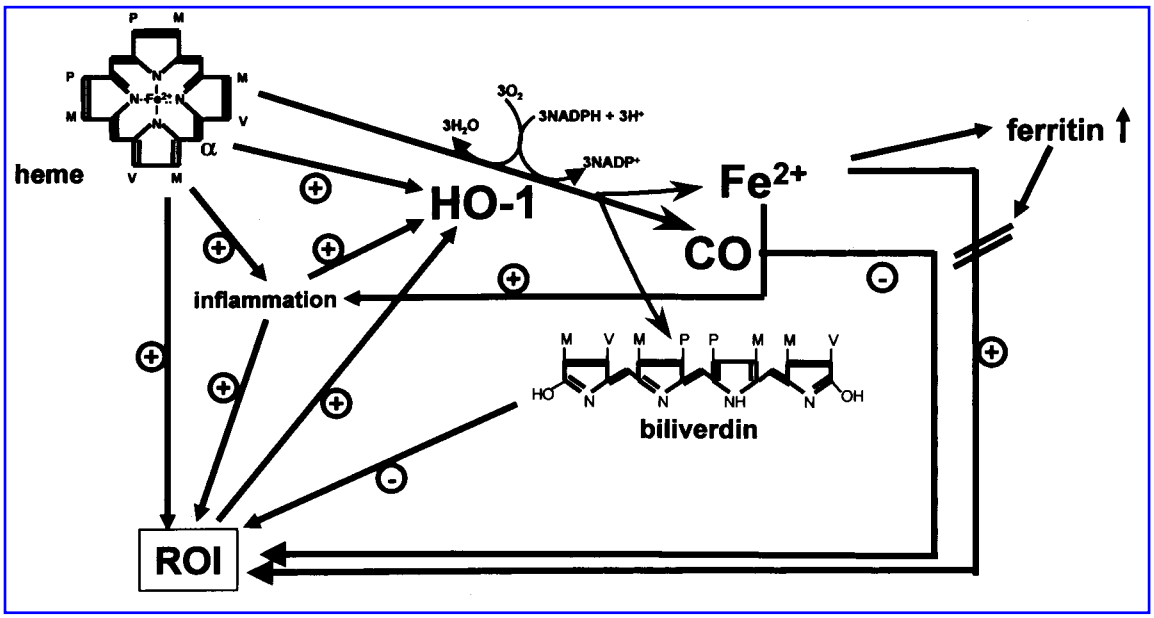

FIG. 1. HO pathway and role in the hepatic response to oxidative stress. ROI, reactive oxygen intermediates.

in the pericentral and midzonal region of the liver acinus, expression upon $CoCl_2$ challenge was restricted to the periportal region of the acinus (4) (Fig. 2). Thus, the acinar and cell type-specific expression pattern of HO-1 with these different stress events extends the concept of ROS as triggers of HO-1 gene expression to the sublobular level in the intact rat liver *in vivo*.

Although regulation of HO-1 gene expression by the redox-sensitive transcription factors AP-1 and NFκB has been an active area of research, evidence suggests that the HO-1 pathway might conversely affect these transcriptional activators. Induction of HO-1 in the rat liver in a model of acetaminophen-induced hepatotoxicity was associated with a concomitant increase of NFκB binding activity, which was markedly reduced by the false substrate SnPP-IX of the HO pathway (5).

BIOLOGICAL FUNCTIONS OF THE HO PATHWAY: HEME CATABOLISM AND PRODUCTS IN THE SEARCH OF FUNCTION

Due to the potential toxic effects of free heme, a meticulous balance between its synthesis and catabolism is crucial to ensure cellular homeostasis. Thus, HO has classically been viewed exclusively as a heme-degrading enzyme system, and heme itself has long been recognized as a potent inducer of HO-1 gene expression in various tissues, including the liver (84). The products of this pathway, *i.e.,* biliverdin, CO, and iron, traditionally received little attention, primarily reflecting the fact that their biological functions were at best obscure. Characterization of some biological activities of the products, along with the observation that the isoenzyme HO-1 is highly inducible and identical to the major 32-kDa heat shock (stress) protein hsp32 (31, 72), has prompted a flurry of studies addressing the role of HO-1 and most notably its reaction products in the hepatic stress response under acute (6, 37, 63, 85) and chronic (14, 47) pathophysiological conditions.

The observations that almost all of these stimuli, including the substrate heme, are linked by their ability to provoke oxidative stress and that bile pigments can function as endogenous antioxidants have supported a role for HO-1 and its products biliverdin/bilirubin in the adaptive response to oxidative stress (2). Hepatic oxidative stress may occur due to a wide variety of stimuli, including such diverse conditions as metabolism of xenobiotics (26) and liver transplantation (48, 49). Among these stimuli, low-flow ischemia and reperfusion

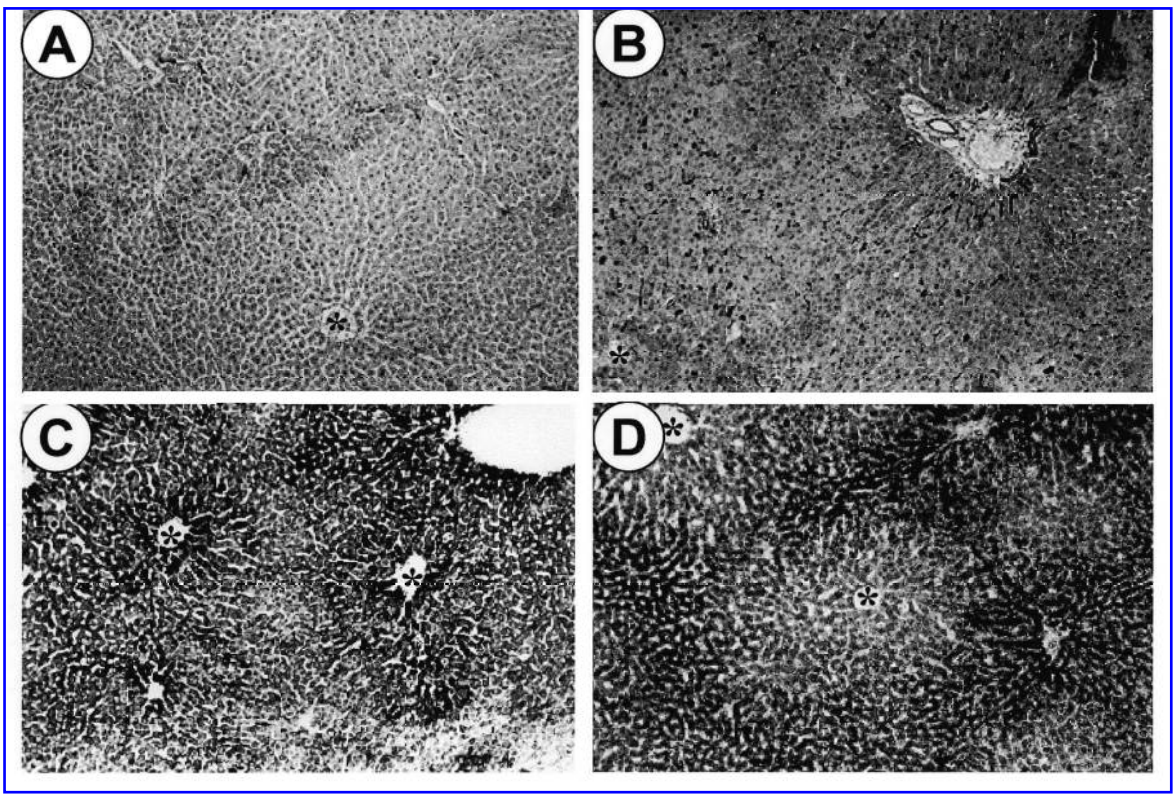

FIG. 2. Acinar distribution and cell type-specific expression pattern of HO-1 in the normal and stress-exposed rat liver as assessed by immunohistochemistry. Liver sections were obtained from normal rats (**A**), or 6 h after infliction of a stress event, *i.e.,* (**B**) LPS challenge (1 mg/kg body weight), (**C**) glutathione depletion with phorone (100 mg/kg body weight) and buthionine sulfoximine (2 mmol/kg body weight), and (**D**) $CoCl_2$ injection (300 μmol/kg body weight). HO-1 immunoreactive protein is restricted to Kupffer cells in the periportal region of the liver under physiological conditions, whereas the gene is inducible in hepatocytes as well as in nonparenchymal cells of the sinusoid: LPS leads to specific induction in Kupffer cells (B), glutathione depletion leads to a *de novo* synthesis in hepatocytes in the pericentral region (C), whereas $CoCl_2$ induces HO-1 in periportal hepatocytes (D). Asterisks indicate central venules.

secondary to hemorrhagic shock and resuscitation is a particular frequent clinical problem (62). This condition, also referred to as "ischemic hepatitis" or "shock liver," results in a typical biphasic injury pattern characterized by an early rise in serum transaminases followed by an increase in serum bilirubin. Previous work from our laboratory indicated that the moderate induction of HO-1 (approximately a 10–15-fold induction of mRNA and protein in the liver) in experimental models of hemorrhagic shock and subsequent resuscitation reflects an adaptive response to ROS formation (64), is attenuated by Kupffer cell depletion (56), and confers delayed protection (55, 63). Blockade of the pathway with the false substrate SnPP-IX increased the histomorphometrically assessed area of pericentral hepatocellular damage, as well as the release of α-glutathione *S*-transferase (α-GST) (63), a sensitive and specific marker of hepatocellular injury (61). Consistent with an antioxidant activity (presumably of bile pigments), coadministration of trolox (a potent antioxidant) with SnPP-IX attenuated the release of α-GST in these experiments, although it failed to attenuate the area of pericentral damage (63). These observations lend support to the notion that different modes of protection of HO-1 and its products are involved and may reflect a protective effect of the antioxidants formed primarily in the well perfused areas of the liver after resuscitation from hemorrhage. Although the protective actions of bile pigments *in vitro* and *in vivo* during heme degradation have attracted attention lately (11, 22, 40, 76, 77), it is obvious that the long known potential toxic effects of bile pigments are likely to limit the beneficial actions of biliverdin/bilirubin to a rather narrow threshold of overexpression of HO-1. The potential toxic actions of bile pigments range from itching as observed with jaundice of various origin to severe neuronal damage primarily of basal ganglia as observed in severe icterus neonatorum (kernicterus; 70). Although neurons seem to be particularly susceptible to the toxic actions of bile pigments, a more general toxic action through damage of lipid bilayers of biological membranes is assumed to reflect the molecular mechanism by which bile pigments act toxic (93). Thus, these effects might also contribute to hepatocellular injury in the case of substantial overexpression of HO-1 in liver injury. However, this has not been studied specifically to date.

Iron is released in equimolar amounts when heme is degraded to yield biliverdin and CO. As iron, like other transition metals, catalyzes the formation of reactive oxygen intermediates, most notably the hydroxyl radical (Haber–Weiss or Fenton reaction; 21), it is obvious that this by-product may offset the antioxidative properties of bile pigments if it is formed in sufficient amounts. Thus, HO-1 expression as part of the cellular stress response may exhibit pro- and antioxidant properties (67). Ferritin, representing a cellular storage system for iron, is an acute-phase reactant that is regulated essentially by the same stress events as HO-1, including iron, heme, UV irradiation, and hypoxia/reoxygenation (82, 87). Thus, both stress proteins tend to be up-regulated simultaneously (88). Iron ions and iron regulatory proteins binding to iron-responsive elements in the ferritin gene may explain the cooperative regulation of both genes because HO activity will increase availability of cellular iron. However, the mechanisms that are involved in coexpression of HO and ferritin genes are poorly understood and may involve additional pathways beyond increases in cellular iron due to heme degradation. For instance, in HO-2 knockout mice, ROS may initiate a transcriptional activation of the HO-1 gene, but these animals fail to induce ferritin transcripts simultaneously (12). In any case, evidence suggests that iron ions can synergize with ROS to regulate the expression of oxidative stress response genes, including HO-1 itself (68). Disorders of iron metabolism leading to excessive iron storage, such as hereditary hemochromatosis, may promote a chronic inflammatory response in the liver. As HO-1 seems to be of outstanding importance for iron reutilization in rodents (58) and humans (96), the observed hepatic inflammation in HO-1 knockout mice, as well as in the reported case of human HO-1 deficiency, is likely to result at least in part from iron deposition secondary to impaired reutilization. Whether in turn increased release/deposition of free iron ions due to acute overexpression and increased HO activity may result from induction of the HO-1 gene in the liver *in vivo* [as has been suggested in cultured cells (81)] has not been studied specifically. Consistent with this notion, inhibition of the HO pathway with SnPP-IX attenuated neutrophil accumulation, as well as activation of the transcription factor NFκB in the liver in a model of acetaminophen toxicity, which was characterized by an approximately 30-fold increase of HO-1 immunoreactive protein over sham-injected controls (5). Thus, a substantial increase in HO activity may have a permissive effect on liver inflammation, although HO-1 has been suggested to have antiinflammatory effects under appropriate experimental conditions as well (94).

CO has lately received much attention as a messenger molecule, most notably in neuronal tissue. HO as a potential endogenous source of CO colocalizes with sGC—as a potential target of CO actions—in various neuronal tissues, and inhibition of HO by false substrates or gene knockout may adversely affect functions of the central and peripheral nervous systems (25, 89).

Although CO and NO share some similarities, there are substantial differences between both gaseous monoxides with respect to their mode of action. NO synthesis by the constitutive NO synthase (NOS) isoforms is tightly regulated by physiological stimuli (coupled to Ca^{2+} release), and its half-life is highly limited due to its radical nature leading to reaction with metal ions, ROS, or sulfhydryl groups in the cell. Thus, stimulation of the constitutively expressed NOS isozymes (NOS I, NOS III) leads to a short-lived burst of NO production, which in turn results in a rapid and transient rise in local cyclic GMP levels reflecting an approximately 100–400-fold activation of sGC. The substantial increase in sGC activity is due to binding of NO to the prosthetic heme moiety of sGC, leading to breaking of the proximal His-Fe bond and formation of a 5-coordinated nitrosyl heme complex (32).

In contrast, CO is not a radical species, and its production by HO is not tightly regulated in an "on-off" manner, confounding the hypothesis of a mutual exchangeable role of NO and CO as gaseous activators of sGC. Furthermore, binding of CO to the prosthetic heme group of sGC leads to formation of a 6-coordinated heme complex with intact His-Fe bonds and only an approximately fivefold increase in activity of the $\alpha_1\beta_1$ heterodimeric isoform of sGC (78). However, mechanisms such as sensitization of sGC to CO in biological

systems (15), as well as control of NO production by HO (95), may result in a substantial increase of the impact of the HO pathway for control of cyclic GMP levels. Thus, the functional significance of the HO pathway for control of vascular resistance may be underestimated from *in vitro* studies of activation of the $\alpha_1\beta_1$ heterodimeric isoform of sGC by exogenous CO. With respect to the regulation of liver blood flow and resistance, work from Suematsu and coworkers would suggest that CO rather than NO acts to control hepatic cyclic GMP levels and sinusoidal resistance (79). This activity of the HO pathway is, however, confined to the portal circulation, whereas the hepatic arterial inflow of the liver is subject to control by NOS/NO in the intact rat liver *in vivo* (54).

Similar to the NOS system, which comprises constitutive and inducible isoforms, the HO system is, as discussed earlier, characterized by constitutive and stress-inducible isoenzymes. The stress-induced production of NO by the inducible NOS isoform (NOS II) is independent of Ca^{2+}/calmodulin, which controls NO production by the constitutive NOS isoforms. Thus, substantially higher amounts of NO are produced in a tonic fashion. Work from our laboratory suggests that similarities exist between the stress-inducible NOS/NO and the HO-1/CO pathway (6, 63). Blockade of HO activity with false substrates of the HO pathway produced a moderate, selective, and transient increase in portal vascular resistance, but no decrease in portal blood flow in the normal rat liver. In contrast, a substantial, selective, and lasting increase in portal resistance was observed upon administration of SnPP-IX after transcriptional activation of the HO-1 gene by hemorrhage and resuscitation (6). This augmented pressor response of false substrates of HO in the liver is paralleled by a decrease in portal blood flow and reflects unmasking of a parallel induction of vasoconstrictors, such as endothelin-1 (66). The sensitization of the portal/sinusoidal sites of resistance to false substrates of the HO pathway may reflect, in addition to increased amounts of HO protein due to HO-1 gene expression, increased substrate availability, because cellular injury is likely to increase degradation and turnover of hemoproteins. Although due to similarities between the gaseous monoxides CO and NO sGC has been traditionally considered as the target of cellular actions of CO, alternative modes of action of CO have been suggested. These cyclic GMP-independent effects may include activation of vascular 238pS K_{Ca} (92) and 105pS K_{Ca} (30) channels rendering smooth muscle cells less responsive to the actions of vasoconstrictors.

Although the mechanisms have not been fully elucidated, data available to date are consistent with a permissive effect of the HO/CO system for liver blood flow after (oxidative) stress events, which contributes to the net protecting effect in these stress models. Pannen *et al.* (55) and Rensing *et al.* (63) have demonstrated aggravation of liver injury by blockade of HO activity with SnPP-IX as reflected in accumulation of reduced pyridine nucleotides indicative of tissue hypoxia, impaired bile flow, and increased leakage of α-GST along with histological damage after induction of the HO-1 gene expression due to low-flow ischemia/reperfusion *in vivo*. However, improvement of blood flow is unlikely to reflect the single mode of protection: Although coadministration of an antioxidant attenuated the leakage of hepatocellular enzymes into plasma, the morphometrical analysis of the area of pericentral necrosis as a hallmark of impaired liver blood flow was unaffected. These observations are consistent with protection of hepatocytes in the areas with maintained perfusion through a different mechanism.

These data would suggest that both antioxidant properties (presumably via biliverdin formation) and improved blood flow (presumably via CO formation) contribute to the salutary effects of HO-1 gene expression. Impairment of flow and ensuing ischemia are likely to increase hepatocellular damage via a necrotic pathway. Recent evidence would suggest that CO may additionally confer protective effects via antiinflammatory (53, 94) and/or antiapoptotic mechanisms (69).

FUNCTIONAL SIGNIFICANCE OF UP-REGULATED HO-1 GENE EXPRESSION: PROTECTIVE AND DETRIMENTAL MODES OF ACTION

Studies using HO-1 knockout mice, as well as the report of the first human case of HO-1 deficiency, suggest an important role for the inducible HO isozyme already under physiological conditions. Mice lacking HO-1 exhibited an incapacity to modulate body iron stores properly and were more susceptible to hepatic injury (59), suggesting an important role of HO-1 in iron homeostasis under normal and stress conditions (58). In addition, recent evidence suggests that stress conditioning including HO-1 gene expression, as well as HO-1 gene transfer, can render the liver less susceptible to subsequent stress events (1). Consistent with these observations, blockade of HO activity by SnPP-IX or ZnPP-IX has been shown to negatively affect liver blood flow (6), energy metabolism (55), hepatocellular secretory function (37), and hepatocellular integrity (63) in a variety of stress models. Although the bulk of literature available to date would suggest that HO-1 gene expression confers hepatocellular protection in a variety of clinically relevant injury models (23), it is obvious that all products of this pathway may cause injury under appropriate conditions. Iron, bile pigments, and CO have been known as potent toxins long before cytoprotective properties have been suggested for the HO pathway, and there is evidence to suggest that protective properties of this pathway are restricted to a rather narrow threshold of overexpression (81). Although cytoprotection by prior exposure of the cell to noxious stimuli is well known, the mechanisms by which toxins might induce resistance to subsequent cellular injury are very much a matter of conjecture. Although evidence available to date would suggest that HO-1 is neither exclusively cytoprotective nor cytotoxic, transcriptional activation of the HO-1 gene clearly reflects a hallmark of the hepatic oxidative stress response. Thus, unraveling of the biological actions of the products of the HO pathway might help to elucidate some of the mechanisms contributing to hepatic stress tolerance.

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ABBREVIATIONS:

ALA, δ-aminolevulinic acid; AP-1, activator protein-1; CO, carbon monoxide; α-GST, α-glutathione *S*-transferase; HO, heme oxygenase; LPS, lipopolysaccharide; NFκB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; SnPP-IX, tin protoporphyrin-IX; ZnPP-IX, zinc protoporphyrin-IX.

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