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Heme oxygenase-1 and acute kidney injury

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Abstract

Purpose of review—Heme oxygenase activity, possessed by an inducible heme oxygenase-1 (HO-1) and a constitutive isoform (HO-2), catalyzes the conversion of heme to biliverdin, liberates iron, and generates carbon monoxide. First shown in acute kidney injury (AKI), HO-1 is now recognized as a protectant against diverse insults in assorted tissues. This review summarizes recent contributions to the field of HO-1 and AKI.

Recent findings—Recent findings elucidate the following: the transcriptional regulation and significance of human HO-1 in AKI; the protective effects of HO-1 in age-dependent and sepsis-related AKI, cardiorenal syndromes, and acute vascular rejection in renal xenografts; the role of heme oxygenase in tubuloglomerular feedback and renal resistance to injury; the basis for cytoprotection by HO-1; the protective properties of ferritin and carbon monoxide; HO-1 and the AKI–chronic kidney disease transition; HO-1 as a biomarker in AKI; the role of HO-1 in mediating the protective effects of specific cytokines, stem cells, and therapeutic agents in AKI; and HO-2 as a protectant in AKI.

Summary—Recent contributions support, and elucidate the basis for, the induction of HO-1 as a protectant against AKI. Translating such therapeutic potential into a therapeutic reality requires well tolerated and effective modalities for upregulating HO-1 and/or administering its products, which, optimally, should be salutary even when AKI is already established.

Keywords

acute kidney injury; acute renal failure; cytoprotection; heme oxygenase-1

INTRODUCTION

Heme proteins are present in virtually all intracellular and extracellular compartments and are broadly involved in cellular homeostasis [1–6]. These proteins can be denatured and destabilized, however, when homeostatic disturbances are imposed by ischemic,

Conflicts of interest

There are no conflicts of interest.

nephrotoxic, and inflammatory insults. Such destabilization of heme proteins weakens the union between their heme and globin moieties, and may eventuate in the release of heme. This loss of heme from heme proteins further disrupts cellular hemostasis because free heme is prooxidant, proinflammatory, and proapoptotic [1–6]. Cellular levels of heme must thus be quite closely controlled, and this governance is carried out by heme oxygenase.

Heme oxygenase converts heme to biliverdin via a reaction that produces carbon monoxide and liberates iron (Fig. 1) [1–6]; bile pigments and carbon monoxide, in low concentrations, are cytoprotective molecules that widely influence signaling pathways, whereas iron links heme oxygenase to ferritin and other participants in iron homeostasis. Heme oxygenase (HO)-1 and HO-2 are the inducible and constitutive isoforms with heme oxygenase activity [1–6].

The cytoprotective properties of HO-1 were first recognized in the kidney, specifically, in a model of heme protein-induced AKI [7]. HO-1 was subsequently shown to be a protectant in AKI induced by cisplatin [8,9], ischemia-reperfusion [10,11], lipopolysaccharide (LPS) [12], and urinary tract obstruction [13], and following renal transplantation [14,15]. Reduction in renal injury when HO-1 is induced originates in varying degrees from the tripartite protective processes elicited by HO-1: the removal of an endogenous toxicant (heme); the procurement of cytoprotectants (bile pigments, carbon monoxide, and ferritin); and the engagement of mechanisms that safeguard iron homeostasis [1–6]. These processes lead to vasorelaxant, antioxidant, anti-inflammatory, and antiapoptotic effects that are salutary in AKI.

Two additional considerations are broadly germane to the induction of HO-1 in AKI. The first consideration is that HO-1 is one of the most readily inducible genes, as it responds to an array of stimuli and insults that involve, among others, reactive oxygen and nitrogen species, cytokines, ischemia, hypoxia, irradiation, heavy metals, various metabolites, hemodynamic stress, and therapeutic agents [1–6]. Several transcription factors have been generally implicated in the induction of the HO-1 gene and these include nrf2, nuclear factor κ B, and AP-1 [1–6]; the specific signaling pathways and transcription factors involved in inducing HO-1 in AKI are under substantial investigation and may depend on the type of AKI, the severity of the renal insult, and the specific temporal phase during the time course of AKI. Moreover, transcriptional control of the HO-1 gene may differ among species, and discussed below are novel findings regarding transcription of the human HO-1 gene in AKI. The second consideration is that the induction of HO-1 can generate products and elicit biochemical consequences that can be cyto-toxic. For example, carbon monoxide, in relatively larger quantities, is toxic through mechanisms that include the avid binding of carbon monoxide to the heme prosthetic group in heme proteins, with the attendant dysfunction of these proteins; increased amounts of iron released from heme by heme oxygenase activity, if inadequately sequestered or transported, can catalyze oxidative stress. Thus, the remarkable and intriguing virtue of the induction of HO-1 in AKI is that such induction— in its timing, intensity, duration, and location —generally protects rather than injures the kidney, and facilitates rather than delays the process of recovery from the initial renal insult.

Recent salient contributions to the field of HO-1 and AKI are now reviewed.

THE FUNCTIONAL SIGNIFICANCE AND REGULATION OF HUMAN HEME OXYGENASE-1 IN MURINE ACUTE KIDNEY INJURY

A novel transgenic mouse was recently generated that contained a bacterial artificial chromosome (BAC) expressing human HO-1 mRNA and protein [16^{***}]. Breeding these mice with HO-1^{-/-} mice generated HO-1^{-/-} mice expressing the human HO-1 gene. This restitution of the HO-1 gene (human) into a hitherto HO-1 deficiency state (murine) attenuated the phenotypic features of murine HO-1 deficiency, including susceptibility to nephrotoxic AKI [16^{***}]. These studies demonstrate the cytoprotective nature of human HO-1 and its capacity to functionally substitute for the missing murine gene. This mutant mouse also facilitates the study of the regulation of the human HO-1 gene *in vivo*, an important consideration because regulation of the mouse and human genes may differ in several ways including the response to specific stressors, key features of the cadmium response element, and the presence of certain intronic enhancers [17,18]. Critical elements in human HO-1 gene transcription, as studied *in vitro*, include the role of chromatin looping in facilitating the involvement of key regulatory regions; the function of specificity factor (Sp1) in configuring chromatin and transcribing the gene; and modulation by either activators (JunB and USF 1 and 2) or repressors (JunD) [19–21]. Remarkably, studies in the humanized HO-1 BAC transgenic mouse confirm and refine this in-vitro model by corroborating the involvement of USF 1 and 2, JunB, Sp1 and chromatin looping, and by recognizing the contribution of CCCTC-binding factor in such transcriptional regulation [16^{***}]. This mutant mouse thus facilitates the study of the significance and regulation of human HO-1 in AKI, and thus translational studies of HO-1 in human AKI.

HEME OXYGENASE-1 AND AGE-DEPENDENT SENSITIVITY TO ACUTE KIDNEY INJURY

Age increases the risk for AKI. Following ischemia-reperfusion, aged mice, compared with young mice, exhibit worse renal injury and less renal induction of HO-1, especially in the medulla [22]. The administration of heme arginate to aged mice upregulates HO-1 mainly in cortical tubules and in medullary interstitial macrophages, while concomitantly mitigating the age-dependent sensitivity to AKI; heme arginate also directly induces HO-1 in macrophages *in vitro* [22]. Aged mice depleted of macrophages do not evince HO-1-expressing, medullary interstitial cells after ischemia-reperfusion, nor are they protected by heme arginate. Thus, blunted induction of HO-1 contributes to the age-dependent increased sensitivity to ischemia-reperfusion, and heme arginate attenuates this sensitivity by inducing HO-1 in the kidney, and in medullary interstitial macrophages in particular [22].

Macrophages in which HO-1 is upregulated by adenoviral strategies also protect against ischemic AKI [23]. Such macrophages, after adoptive transfer, localize in the ischemic rather than the healthy kidney, reduce renal dysfunction, and diminish platelet microthrombi [23]. The protective effects of these macrophages likely reflect their elicited anti-inflammatory actions and their enhanced capacity to phagocytose apoptotic cells [23].

Macrophages in which HO-1 is upregulated thus provide a strategy to reduce the risk for ischemic AKI in the elderly and other susceptible patient populations.

HEME OXYGENASE, TUBULOGLOMERULAR FEEDBACK, AND RESISTANCE TO ACUTE KIDNEY INJURY IN THE REMNANT KIDNEY

Both HO-1 and HO-2 isoforms are present in the macula densa of the healthy kidney, and the combined heme oxygenase activity inhibits tubulo-glomerular feedback (TGF) [24,25]. Such inhibition prevents vasoconstriction of the relevant afferent arteriole when there is increased delivery of salt to the macula densa, thereby preserving glomerular filtration rate (GFR). This suppressive effect of heme oxygenase activity on TGF reflects the actions of its products; carbon monoxide suppresses TGF via soluble guanylate cyclase, whereas biliverdin inhibits TGF by scavenging superoxide anion, the latter known to augment TGF [24,25].

This suppressive effect of heme oxygenase on TGF may be relevant to AKI for at least two reasons. First, impaired proximal reabsorption of sodium in AKI increases sodium delivery to the distal nephron; in this setting an intact heme oxygenase system would interrupt afferent arteriolar vasoconstriction, thereby maintaining blood flow, GFR, and sodium excretion. Second, resistance to ischemic AKI occurs in renoprival states, that is, in part, heme oxygenase-dependent [26^{***}]. Subtotally nephrectomized rats, subjected to ischemic AKI, exhibit less histologic injury and a blunted fall in GFR [26^{***}]. TGF is suppressed in renoprival states and this likely explains the greater preservation of single nephron GFR and whole kidney GFR, and the underlying resistance to ischemia-reperfusion. The involvement of heme oxygenase in such resistance reflects, at least in part, its recognized suppressive effect on TGF [24,25,26^{***}].

HUMAN HEME OXYGENASE-1 AND XENOTRANSPLANTATION-ASSOCIATED ACUTE KIDNEY INJURY

Acute vascular rejection causes AKI in xenografts. At least two groups have generated transgenic pigs expressing human HO-1 in the kidney and other organs [27,28^{***}]. Fibroblasts from organs of these transgenic pigs are resistant to proapoptotic stressors, and exhibit a blunted proinflammatory response to LPS or TNF α [28^{***}]. Aortic endothelial cells isolated from another human HO-1 transgenic porcine model resist TNF α -induced inflammation, TNF α -induced cell death, and interferon- γ -elicited expression of major histocompatibility complex (MHC) class II [27]. Kidneys from these transgenic pigs, compared with wild-type kidneys, when perfused *ex vivo* with human blood, exhibit greater duration of perfusion, and do not evince thrombotic microangiopathy [27]. Thus, human HO-1 expression in pigs may render porcine kidneys resistant to AKI induced by acute vascular rejection.

HEME OXYGENASE-1 AND SEPSIS-ASSOCIATED THROMBOTIC MICROANGIOPATHY

As shown previously, deficiency of HO-1 promotes thrombosis in the injured vasculature [29,30], and products of heme oxygenase such as carbon monoxide are anticoagulant [31].

Recent studies demonstrate the protective effects of HO-1 in thrombotic microangiopathy (TMA)-associated AKI that occurs in sepsis induced by cecal ligation and puncture [32[¶]]. This sepsis model fosters a procoagulant state, diminishes plasma levels of activated protein C (APC), and decreases renal expression of thrombomodulin and endothelial protein C receptor (EPCR) [32[¶]]. Pretreatment with hemin augments glomerular HO-1 expression and renal expression of thrombomodulin and EPCR, while reducing renal dysfunction, glomerular TMA, and the procoagulant state; hemin also increases plasma levels of APC in this model [32[¶]]. These effects of hemin, coupled with the converse effects when heme oxygenase is inhibited, support a protective role of HO-1 in sepsis-induced TMA and AKI [32[¶]].

HEME OXYGENASE-1 AND ACUTE KIDNEY INJURY DUE TO CARDIORENAL SYNDROMES

In a murine model of cardiorenal syndrome induced by myocardial infarction, renal dysfunction and histologic injury are reduced when HO-1 is upregulated in the kidney; this protective effect is attenuated when heme oxygenase activity is concomitantly inhibited [33[¶]]. Interestingly, this model of the cardiorenal syndrome causes less severe AKI when created in T-lymphocyte-suppressed severe combined immune deficiency (SCID) mice; and in this latter setting the nephroprotective effect of HO-1 is enhanced [33[¶]]. Induction of HO-1 thus safeguards the kidney following cardiac dysfunction, especially so when T-lymphocytes are suppressed.

HEME OXYGENASE-1 AND THE CELL BIOLOGY OF CYTOPROTECTION

Autophagy can be either a cytoreductive or a cytoprotective process. As a cytoprotective process, autophagy cordons off, digests, and removes injured organelles. However, inordinate or dysregulated autophagy jeopardizes cell survival, and occurs when HO-1 is deficient [34]. For example, kidneys from HO-1^{-/-} mice, compared with HO-1^{+/+} mice, exhibit more abundant autophagosomes in the unstressed state and when stressed by cisplatin, a prooxidant nephrotoxin; conversely HO-1 over-expression in epithelial cells retards the evolution of the autophagic response elicited by cisplatin [34]. The inhibitory effect of HO-1 on autophagy may reflect its antioxidant effect and/or its suppressive effect on beclin, a protein fundamentally involved in autophagy [34]. Interestingly, HO-1 is upregulated in renal cancer cells where it exerts anti-apoptotic and antiautophagic effects [35,36]. In these cells, HO-1 inhibits autophagy by inhibiting expression of beclin-1 and LC3B-II, and fostering the binding of beclin-1 with autophagy-suppressing proteins such as rubicon [36].

Organelle-specific cytoprotective effects of HO-1 are of increasing interest. Mitochondria generate and are injured by oxidants during ischemic and nephrotoxic insults, and such mitochondrial dysfunction contributes to AKI [37[¶]]. Mitochondria do not normally express HO-1, but when renal epithelial cells are engineered to express HO-1 in mitochondria, these cells become resistant to hypoxia-induced cell death and exhibit greater preservation of mitochondrial membrane potential and content of specific intermediates of the TCA cycle

[37¹¹]. Thus, targeted expression of HO-1 at organelles such as mitochondria can interrupt site-specific processes that contribute to AKI.

HEME OXYGENASE-1 AND CYTOPROTECTIVE MEDIATORS

Ferritin synthesis is increased when HO-1 is induced, thereby providing storage for iron released from heme. A novel mutant mouse was recently developed wherein renal proximal tubules lacked expression of ferritin H-chain, the chain that not only binds iron but also interrupts its redox cycling [38¹²]. Such deficiency of ferritin exacerbated heme protein-induced and cisplatin-induced AKI and attendant mortality, even though there was greater HO-1 induction in these mutant mice [38¹²]. Additionally, these studies demonstrate that renal expression of ferritin, the major iron-binding protein, elicits renal expression of ferroportin, the major iron-transporting protein [38¹²]. Thus, independent of HO-1, ferritin exerts a cytoprotective function in AKI, and itself recruits additional proteins, such as ferroportin, in safeguarding iron homeostasis in AKI.

Carbon monoxide is nephroprotective in low doses [39,40]. Studies in a porcine model of cardiopulmonary bypass (CPB) demonstrate that the inhalation of carbon monoxide, prior to CPB, improves renal function, lessens histologic injury, and activates heat shock protein (HSP)-70 [41]. Pharmacologic inhibition of the heat-shock response attenuates the protective effects of carbon monoxide, thereby demonstrating the role of HSP-70 and the heat-shock response in mediating this beneficial effect of carbon monoxide [41].

TRANSITION FROM ACUTE KIDNEY INJURY TO CHRONIC KIDNEY DISEASE

Deficiency of HO-1 increases not only the sensitivity to AKI but also the likelihood that chronic kidney disease (CKD) occurs after acute renal insults [42,43]. Following an acute insult, HO-1 is rapidly induced but its expression subsides before renal recovery fully occurs; such abatement in HO-1 expression may allow the continued expression of proinflammatory and fibrogenic genes [42–44]. In this regard, HO-1 deficiency promotes epithelial–mesenchymal transition (EMT), a process that may underlie the transition of AKI to CKD [45]. For example, HO-1^{-/-} mice, following acute urinary tract obstruction, demonstrate enhanced influx of macrophages, interstitial fibrosis, and tubular expression of transforming growth factor (TGF)- β 1, α -smooth muscle actin, and S100A4 [45]; HO-1 deficiency also exaggerates the appearance of these and other markers of EMT in TGF- β 1-treated proximal tubular cells [45]. The risk for CKD following AKI may thus be reduced by sustained HO-1 expression following AKI.

HEME OXYGENASE-1 AS A BIOMARKER IN ACUTE KIDNEY INJURY

In models of AKI – ischemia-reperfusion, nephrotoxic, and obstructive – HO-1 mRNA and protein are induced in the kidney, and HO-1 protein is detected in plasma and in urine within 4 h; such plasma and urinary levels of HO-1 mirror the profile of induction of HO-1 mRNA in the kidney [46¹³]. Extracellular presence of HO-1 also mirrors cellular HO-1 expression when HO-1 is induced in tubular epithelial cells by iron. In ill patients with AKI, plasma and

urinary HO-1 levels are increased, a finding not observed in ill patients without AKI, or in patients with CKD [46^{***}]. These findings, in aggregate, suggest that plasma and urinary HO-1 levels may serve as a biomarker for human AKI [46^{***}].

HEME OXYGENASE-1 AND NEPHROPROTECTIVE CYTOKINES

Hepatocyte growth factor (HGF) exerts cytoprotective effects in the injured kidney. In LPS-treated mice, recombinant human HGF (rh-HGF) reduces AKI, lung injury, and mortality [47], while fostering the activation of c-Met (the receptor for HGF) and induction of HO-1 in the kidney and lungs. Inhibiting heme oxygenase abrogates these protective effects of rh-HGF and its suppression of inflammatory responses, thereby indicating that HO-1 contributes to the protection afforded by rh-HGF in this model of sepsis [47].

Granulocyte colony-stimulating factor (G-CSF), a mitogenic and a mobilizing stimulus for bone marrow cells, reduces AKI, in part, by recruiting these cells and facilitating their paracrine effects in the injured kidney. An additional mechanism involves induction of HO-1 by G-CSF; G-CSF induces HO-1 in the kidney *in vitro* and *in vivo*; G-CSF reduces renal injury and promotes survival in heme protein-induced AKI; G-CSF-treated renal epithelial cells are resistant to heme-induced apoptosis *in vitro*; and inhibiting heme oxygenase activity attenuates these protective effects of G-CSF *in vitro* and *in vivo* [48].

Adiponectin, a cytokine produced by white fat, exerts anti-inflammatory and vasoprotective effects. Plasma levels of adiponectin decrease following ischemic AKI, and when administered prior to ischemia-reperfusion, adiponectin decreases apoptosis and inflammation and protects against AKI [49]. Adiponectin induces HO-1 in renal epithelial cells *in vitro* and augments renal induction of HO-1 following ischemia-reperfusion; inhibiting heme oxygenase activity compromises the antiapoptotic effects of adiponectin *in vitro* [49]. These findings suggest that the renal protective effects of adiponectin are channeled through HO-1.

HEME OXYGENASE-1 AND NEPHROPROTECTIVE STEM CELLS

Mesenchymal stem cells (MSC) offer a therapeutic strategy in human AKI. Studies in cisplatin-induced AKI demonstrate that the protective properties of MSC rely on HO-1 because conditioned media from MSC obtained from HO-1^{+/+} mice, but not from MSC obtained from HO-1^{-/-} mice, reduce such injury [50]. Production of angiogenic (and potentially nephroprotective) growth factors (such as SDF-1, VEGF, and HGF) by MSC, along with the angiogenic capability of MSC, both require HO-1, and these proangiogenic effects of HO-1 in MSC likely contribute to the nephroprotective effects of MSC [50].

Adipose-derived MSC reduce ischemic AKI when administered after ischemia-reperfusion, an effect ascribed to the induction of HO-1 and other antioxidant and anti-inflammatory genes [51]. These protective effects are enhanced by cyclosporine [51], an agent known to reduce oxidative stress and attenuate ischemia-reperfusion injury in other organs.

HEME OXYGENASE-1 AND NEPHROPROTECTIVE DRUGS

Statins may reduce the risk of human AKI [52,53]. Cerivastatin induces HO-1 in monocytes *in vitro*, and when administered prior to ischemia-reperfusion, cerivastatin augments renal induction of HO-1 (mainly in interstitial monocytes/macrophages) and reduces ischemic AKI; inhibiting heme oxygenase activity attenuates this protective effect [54]. Statin-induced HO-1 expression can elicit an anti-inflammatory phenotype in monocytes/macrophages, which may underlie their beneficial effect in AKI [54].

Fenoldopam, a vasorelaxant dopamine agonist, induces HO-1 in proximal tubular epithelial cells and protects against cell death caused by cold-hypoxia; interrupting HO-1 expression vitiates such protection [55]. Prior exposure of syngeneic rat kidney transplants to fenoldopam increases kidney HO-1 expression and reduces cold ischemia-induced kidney damage assessed at 24 h [55]. Studies undertaken in HO-1^{+/+} and HO-1^{-/-} mice corroborate the role of HO-1 in mediating the protective effects of fenoldopam [55].

Bardoxolone methyl was once regarded as a promising drug in human diabetic nephropathy based on its capacity to induce nrf2 and nrf-2-dependent genes such as HO-1; this promise was vitiated by subsequently noted adverse effects. Studies *in vivo* demonstrate that bardoxolone induces HO-1 and other cytoprotective genes and protects against ischemic and nephrotoxic insults by suppressing renal inflammation and cell death [56].

HEME OXYGENASE-2 AS A PROTECTANT IN ACUTE KIDNEY INJURY

The bulk of heme oxygenase activity in the unstressed kidney arises from HO-2. Unlike HO-1 expression that entails an obligatory temporal delay, HO-2 is already expressed in the kidney when exposed to acute insults. Indeed, recent studies in HO-2^{+/+} and HO-2^{-/-} mice demonstrate that HO-2 protects against heme protein-induced AKI [57]. Interestingly, as shown in other tissues, the protection afforded by the heme oxygenase system may involve not just heme oxygenase activity but also the specific cellular effects of the HO-1 and HO-2 isoforms, which are distinct proteins [58,59].

CONCLUSION

The major actions of HO-1 include the degradation of heme, the procurement of cytoprotectants (carbon monoxide, bile pigments, and ferritin), and the engagement of iron-handling proteins. These chemically disparate actions of HO-1 exert broad-based, far-ranging cellular effects, thereby positioning HO-1 and its products as hubs in the nodal network that safeguard cellular homeostasis in stressed tissues [4,60].

Studies on HO-1 and AKI, including those surveyed here, support a therapeutic approach for human AKI based on the induction of HO-1. Translating such a therapeutic potential into a therapeutic reality faces at least four major challenges [4,60]. First, HO-1 induction usually occurs as a countervailing response to cellular stress, and thus clinically viable modalities that effectively induce HO-1 should do so without incurring, either antecedently or concomitantly, cell injury. Second, products of HO-1 are protective at lower doses, but cytotoxic at higher doses; an approach based on administering these products has to be

deployed within a certain, yet often vaguely defined, therapeutic window. Third, the optimal duration of induction of HO-1 is a challenging issue as sustained HO-1 expression can be injurious, whereas short-lived HO-1 expression may be ineffective. Fourth, clinical AKI is a relatively delayed manifestation of preceding renal insults, and whether added induction of HO-1 and/or provision of its products can succor the kidney in which injury is already established remains, to date, largely unanswered and unexplored.

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KEY POINTS

- Expression of human HO-1 gene and protein in mice protects against murine AKI.
- HO-1 can protect against AKI that arises from age-dependent renal sensitivity, xenograft acute vascular rejection, the cardiorenal syndrome, and sepsis.
- HO-1 suppresses autophagy and can confer organelle-specific protection.
- HO-1 may be a biomarker for AKI.
- HO-1 provides a common pathway for the protective effects of certain cytokines, stem cells, and therapeutic agents.

FIGURE 1.

Schema depicting the biochemical actions of heme oxygenase. Elevations in cellular content of heme can occur from either destabilization of heme proteins or increased heme synthesis. Heme oxygenase catalyzes the conversion of heme to biliverdin via a reaction that requires NADPH and oxygen. This reaction liberates iron and produces carbon monoxide. Two proteins possess heme oxygenase activity, the inducible isoform, HO-1, and the constitutive isoform, HO-2. Biliverdin is subsequently converted to bilirubin via biliverdin reductase in an NADPH-requiring reaction. CO, carbon monoxide; HO-1, heme oxygenase-1; HO-2, heme oxygenase-2; Fe, iron.