Human AKI and Heme Oxygenase-1

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Findings derived from animal models of AKI gain clinical credence and appeal when translational studies corroborate their occurrence in human AKI. In the current issue of JASN, Zager et al.1 take important steps in addressing the clinical applicability of the conclusion drawn from animal models that induction of heme oxygenase-1 (HO-1) is a protective response in AKI.

The major heme-degrading mechanism in tissues, heme oxygenase has its origin in studies probing the metabolic fate of hemoglobin during the culling of senescent erythrocytes by the reticuloendothelial system.2 It was then realized that there were two isoforms with heme oxygenase activity:3,4 the constitutive isoform, HO-2, and the inducible isoform, HO-1; the latter was identified as a cytoprotective gene in a model of AKI induced by heme proteins.5 Subsequently, induction of HO-1 was recognized as a protective response that can occur in all organs and tissues and against virtually any insult.3,4,6–10

At least four features of HO-1 underlie its salutary effects in stressed tissues.11,12 First, HO activity generates three chemically distinct products—carbon monoxide, bile pigments, and iron—each of which can participate in specific cellular processes; induced HO-1 thus transmits broad-based and far-ranging signals through its tripartite products and their respective downstream effects. Second, all products of HO activity are involved in a number of homeostatic mechanisms; induced HO-1 thus readily communicates with networks that influence cell survival. Third, ischemic and toxic insults can destabilize intracellular heme proteins (for example, cytochrome p450), and heme that is released can itself perpetrate cell injury; induced HO-1 thus vitiates secondary pathways of cellular injury mediated by free heme. Fourth, HO-1 is a finely regulated gene readily responsive to diverse stimuli. It rapidly appears in injured cells and recedes as repair and renewal of tissues occur; expression of HO-1 thus occurs when and where needed.

Induction of HO-1 in the kidney consistently occurs in models of AKI and confers a beneficial response.3,11 Whether such induction occurs in human AKI is thus of interest. However, addressing this issue in human AKI is challenging, not only because of the general unavailability of human kidney tissue in human AKI, but also because measurements of HO-1 levels in extracellular fluid venture into largely uncharted areas in the heme oxygenase field. The heme oxygenase literature regards the expression of HO-1 as a cellular phenomenon involving mainly the endoplasmic reticulum; it provides little information on the presence of HO-1 in extracellular compartments and none on the route HO-1 may take to get there.

In addressing this question, Zager et al.1 first determined whether the appearance of HO-1 in plasma and urine would provide a faithful readout of intracellular HO-1 in the injured kidney.1 Their approach quite cleverly exploited the specific features of different models of AKI. In two models characterized by early-onset, sublytic cell injury and necrosis (ischemia and glycerol-induced AKI), immunoreactive HO-1 (by ELISA) was detected in plasma and urine within 4 hours after the insult. In cisplatin-induced AKI, a model characterized by relatively delayed-onset sublytic cell injury and necrosis, plasma and urinary levels of HO-1 were elevated at 24 hours and antedated the increase in BUN. The importance of sublytic cell injury and necrosis, as occurs in these AKI models, in effecting such elevation in plasma and urinary HO-1 was underscored by studies in AKI induced by urinary tract obstruction. Urinary tract obstruction leads to flattening and atrophy of the tubular epithelium, and if epithelial cell death occurs, it primarily involves apoptosis and its containing effect and not necrosis with its spillage of cellular debris; urinary tract obstruction was attended by a lesser rise in plasma and urine HO-1 levels. Studies undertaken in vitro in proximal tubular epithelial cells injured by iron reveal the presence of immunoreactive HO-1 in the extracellular supernatant concomitant with intracellular induction of HO-1. Finally, to address whether the increased plasma levels of HO-1 reflect sources other than the kidney, Zager et al. evaluated HO-1 gene expression in extrarenal organs in glycerol-induced and cisplatin-induced AKI at the 24-hour time point; in these studies, induction of HO-1 in extrarenal organs was not observed. These findings led to the conclusion that HO-1 protein, induced in injured tubular epithelial cells, may either exit across a leaky apical plasma membrane to appear in urine or across a porous basolateral membrane to eventually appear in plasma.

These studies were then followed by measurements undertaken in critically ill patients with and without AKI.1
findings in patients with AKI recapitulate experimental observations; namely, the presence of AKI leads to markedly higher levels of plasma and urinary HO-1 compared with patients without AKI. Moreover, this elevation in plasma and urinary HO-1 in patients with AKI is not observed in patients with CKD or ESRD, thus demonstrating that uremia, when chronically imposed, is not attended by increased levels of plasma HO-1. Thus, the markedly increased concentrations of HO-1 in urine and plasma in human AKI, in conjunction with accompanying analyses in disease models, support the view that HO-1 is induced in the kidney in human AKI.

Zager et al. countenance the possibility that extrarenal production of HO-1 may contribute to HO-1 appearing in plasma. In this regard, induction of HO-1 has been described in the liver within 6 hours in the glycerol model and by 24 hours in the cisplatin model. Presumably, such hepatic HO-1 induction reflects, at least in part, heme proteins delivered to the liver as occurs in the glycerol model or the direct pro-oxidant effects of cisplatin incorporated in the liver. Extrarenal HO-1 production is of particular interest in ischemia-induced AKI because any such induction would reflect long-range effects of localized ischemia and not a direct effect of the imposed insult: induction of HO-1 has been detected in the heart within 4 hours and in the aorta within 24 hours after renal ischemia. Thus, the contribution of the injured kidney to plasma levels of HO-1 may be supplemented by extrarenal sources.

The increased appearance of HO-1 in plasma in AKI seems especially relevant to the concept that AKI instigates renal and systemic inflammation and adverse distant effects. These regional and long-range effects contribute to AKI-associated mortality and involve the elaboration of cytokines, including IL-6. Plasma levels of IL-6 are increased in human AKI and are a predictor of mortality, whereas in murine ischemic AKI, IL-6 is substantially induced and underlies such injury. HO-1 mediates the protective effects of cisplatin incorporated in the liver. Extrarenal HO-1 production is of particular interest in ischemia-induced AKI because any such induction would reflect long-range effects of localized ischemia and not a direct effect of the imposed insult: induction of HO-1 has been detected in the heart within 4 hours and in the aorta within 24 hours after renal ischemia. Thus, the contribution of the injured kidney to plasma levels of HO-1 may be supplemented by extrarenal sources.

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The present findings raise additional lines of inquiry regarding the nature of the immunoreactive HO-1 protein present in plasma and urine—specifically, whether this protein possesses HO activity and whether it exhibits sequence homology with native HO-1 protein. It is notable that the HO-1 protein detected in urine exists as a 16-kDa moiety, whereas intact HO-1 is a 32-kDa protein, consisting of two helical loops. It is possible that this cleavage of HO-1 is incurred by proteolytic enzymes released from injured cells or by hydrogen peroxide, which may attain micromolar levels in urine.

In conclusion, Zager et al. provide the first concerted analysis of HO-1 in plasma and urine in human AKI and elucidate the significance of these findings by their discerning application of relevant in vivo and in vitro models. Such translational analyses, recently used by their laboratory with regard to MCP-1 and AKI, serve to validate or repudiate the clinical applicability of paradigms derived from animal models of AKI. The demonstration that increased amounts of HO-1 appear in the regional and systemic milieu of human AKI raises the possibility that this inducible protein may subserve a protective role in human AKI; additionally, these findings introduce a new candidate for consideration in the biomarker field. Finally, these findings are of therapeutic significance. Novel inducers of HO-1, such as bardoxolone methyl, are not only protective in experimental AKI but also show early promise in human diabetic nephropathy. Based on these and the current findings, such compounds offer the exciting prospect for a new preventive or therapeutic strategy in human AKI.

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DISCLOSURES

None.

REFERENCES


