The Role of Catalytic Iron in Acute Kidney Injury

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What is Catalytic (Labile) Iron, and Why is it Important?

The pathologic effects of iron accumulation in tissue in iron-overload states, such as are described in patients with thalassemia, are widely known. What is new in the field is the recognition that iron plays an important role in the pathophysiology of tissue injury in the absence of systemic iron overload. Critical to iron's importance in biologic processes is its ability to cycle reversibly between its ferrous and ferric oxidation states. This precise property, which is essential for its functions, also makes it very dangerous because free iron can catalyze the formation of free radicals (1), which can damage macromolecular components of the cell.

Although iron is the most abundant transitional metal in the body, labile, or catalytic, iron, which can be measured by several methods (1,2), constitutes only a small fraction of the total iron pool. Labile iron was originally defined as a transitional pool between extracellular and cellular iron and was generally associated with low-molecular-weight chelates. From a pathophysiologic standpoint, however, an iron pool that can participate in redox cycling is important and is therefore often referred to as catalytic iron. There are two broad lines of evidence for the role of catalytic iron in the pathophysiology of disease: That it is increased in disease states and that iron chelators provide a protective effect, thereby establishing a cause–effect relationship. This has been demonstrated in a variety of disease states, including acute and chronic kidney disease, acute myocardial infarction, and neurodegenerative disorders. Thus, its role in disease processes seems to be a common theme of cellular injury.

Catalytic Iron in Nephrotoxic Acute Kidney Injury

During the Battle of Britain, Bywaters and Beall described the first causative association of acute kidney injury (AKI) with skeletal muscle injury. Since then, the spectrum of etiologies for rhabdomyolysis, myoglobinuria, and renal failure has been markedly expanded with the recognition of both traumatic and nontraumatic causes.

There is a marked and specific increase in catalytic iron content (3) in an animal model of myoglobinuric AKI, and an iron chelator provides a protective effect on renal function and on histologic evidence of renal damage (4). Paller (5) also demonstrated that deferoxamine treatment is protective in three models of myoglobinuric renal injury, namely hemoglobin-induced nephrotoxicity, glycerol-induced AKI, and a combined renal ischemia/hemoglobin insult. Similarly, Zager (6), in his studies, demonstrated the protective effect of an iron chelator in myohemoglobinuric injury. Baliga *et al.* (3) showed that cytochrome P450, a group of heme proteins, might be a significant source of iron in this model of AKI. Taken together, these studies implicate a role for catalytic iron in rhabdomyolysis-associated AKI.

Cisplatin is a widely used antineoplastic agent that has nephrotoxicity as a major adverse effect. Exposure of renal tubular epithelial cells to cisplatin results in a significant increase in catalytic iron, and iron chelators significantly attenuate cisplatin-induced cytotoxicity (7). Catalytic iron as measured by the bleomycin assay is markedly increased in the kidneys of rats treated with cisplatin. Administration of an iron chelator in rats provides marked functional (as measured by blood urea nitrogen and creatinine) and histologic protection against cisplatin-induced AKI. Baliga *et al.* (8) also showed that cytochrome P450 might serve as a significant source of catalytic iron in cisplatin-induced nephrotoxicity. These data implicate a critical role for iron in mediating tissue injury in this model of nephrotoxicity.

Nephrotoxicity is a major complication of the use of aminoglycoside antibiotics, including gentamicin. Hydroxyl radical scavengers and iron chelators provide a marked protective effect on renal function and histologic evidence of damage in gentamicin-induced AKI in rats (9). Gentamicin enhances the release of iron from renal cortical mitochondria, suggesting iron-rich mitochondria as a potential source of iron (10).

Hanss *et al.* (11), using a multi-insult model of contrast nephropathy, examined the effect of an iron chelator on renal function. Rabbits pretreated with an iron chelator showed significant protection against a contrast-induced decrease in creatinine clearance, suggesting an important role of catalytic iron in this model. Because the effect of catalytic iron is to increase oxidative stress, it is of interest that experimental evidence exists for the role of oxidants in contrast-induced AKI (12).

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Catalytic Iron in Ischemia-Reperfusion Injury

Ischemia-reperfusion is an important cause of AKI. Baliga *et al.* (13) showed a marked increase in catalytic iron after ischemia-reperfusion injury (IRI), and an iron chelator has been shown to be protective (14). Additional evidence of the role of iron in IRI comes from reports that other types of iron-binding and/or -translocating compounds also provide protection against ischemia. The amount of circulating redox-active iron was shown to increase significantly in an experimental model of IRI, and an infusion of apotransferrin (but not iron-saturated apotransferrin) resulted in a dosage-dependent improvement in renal function after reperfusion (15). Neutrophil gelatinase-associated lipocalin (NGAL), which is an important iron-transporting and -translocating compound, provides additional evidence of the importance of iron in AKI (16). Infusion of NGAL has been demonstrated to be protective against renal IRI (17).

Additional evidence for catalytic iron in IRI is derived from studies of myocardial ischemia. During experimental cardiac ischemic injury, there is a 30-fold increase in catalytic iron (18). The iron chelators deferiprone (19) and deferoxamine have been demonstrated to protect against experimental cardiac IRI. Deferoxamine has been shown to improve outcomes in humans after coronary artery bypass graft surgery (20). These data supporting the importance of iron in the pathogenesis of ischemic injury are compelling.

Human Studies

One should be cautious in extrapolating results from animal studies to humans because clinical trials in AKI based on animal models (*e.g.*, anti-natriuretic peptide and IGF) have failed. Nonetheless, evidence that catalytic iron seems to be involved in a variety of models of AKI suggests that this may be a common mechanism of tissue injury, and limited data from human studies support this notion. Rajapurkar *et al.* (21) in a preliminary study reported that kidney donors undergoing either an intravenous pyelogram or a renal arteriogram have a marked increase in urinary catalytic iron accompanied by evidence of tubular injury as reflected by an increase in urinary alkaline phosphatase and N-acetyl-β-glucosaminidase. In human studies, Drager *et al.* (22) reported a several-fold increase in urinary isoprostane (marker of oxidative stress) after cardiac catheterization.

Hepcidin is a major regulator of iron homeostasis that acts by binding to ferroportin receptors (iron-exporting proteins), leading to intracellular iron sequestration (23,24,25). In a prospective cohort study of individuals undergoing cardiopulmonary bypass surgery, Ho *et al.* (26) reported that a proteomic analysis of urine of individuals who did not develop AKI postoperatively had the presence of two high-intensity peaks. One of these peaks was determined to be hepcidin-25. Haase-Fielitz *et al.* (27) provided support for the utility of hepcidin as an early predictive biomarker of ruling out AKI by demonstrating that higher urinary hepcidin after cardiopulmonary bypass discriminates patients who do not develop AKI or do not need renal replacement therapy. In a subsequent study using an ELISA to validate their earlier proteomic findings quantitatively, Ho *et al.* (28) reported that urinary hepcidin-25 was significantly elevated in patients with *versus* without AKI. These studies, in which hepcidin (which helps to sequester iron) is associated with protection, lend additional support for the role of catalytic iron in AKI. In a comprehensive and thoughtful analysis of the various novel biomarkers that have been examined after cardiopulmonary bypass–associated AKI, Haase *et al.* (29) concluded that free iron–related kidney injury seems to be the unifying pathophysiologic connection for these biomarkers. Using biomarkers that are pathophysiologically linked to the disease process has major therapeutic implications. The availability of iron chelators with favorable adverse effect profiles for short-term use makes them attractive for clinical trials aimed to prevent or treat AKI.

Disclosures

SS has a financial interest in Shiva Biomedical, LLC, which has licensed its technology related to the diagnosis and treatment of kidney disease to CorMedix, Inc. The other authors report to conflict.

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See related article, "Urinary Hepcidin-25 and Risk of Acute Kidney Injury Following Cardiopulmonary Bypass," on pages 2340–2346.