Aging and hemoglobin-induced acute kidney injury

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It is well known that the incidence of acute kidney injury (AKI) increases with advancing age (2). Conceivably, it is related to the age-related functional and structural changes in the kidney that render the elderly population highly susceptible to AKI. Although the relationship between aging and AKI remains somewhat poorly understood, several studies highlight a number of mechanisms that could explain the reason for susceptibility to AKI of older individuals (3,12). In this regard, maladaptation of the defense system against oxidative stress is believed to play a major role in the process of cellular aging. With a compromise in the defense system, such as that exerted by heme oxygenase (HO), it is likely that oxidative stress would increase in the aging kidney, resulting in an increased incidence of AKI.

In an issue of the American Journal of Physiology-Renal Physiology, Nath et al. (7) provide new information in several important and related areas. The first is the recently emphasized risk for AK caused by age, which may be related to the pathobiology of heme oxygenase, a protein that handles oxidative stress. Studies in animal models have commonly used a ischemia-perfusion injury model to investigate this question, but there are few experimental data examining the influence of age on AKI caused by nephrotoxins. This is clinically important given the frequency of AKI caused by nephrotoxicity due to endogenous substances (e.g., hemoglobin due to hemolysis or myoglobin following rhabdomyolysis), administered drugs (e.g., antibiotics and NSAIDS), or administered diagnostic agents (e.g., contrast dye). The importance of the present study is that it provides experimental evidence that supports the notion of age as a risk factor for not only ischemic injury but also toxic insults to the kidney.

Nephrotoxicity involves, at least partly, how a given substance is processed by the kidney, and thus the question arises of whether there are differences as to how hemoglobin is processed in the kidney by aged vs. young mice. With this in mind, Nath et al. (7) undertook an investigation in aged and young mice, and, in fact, this is one of the most detailed studies in this area of research that is currently available. Within this objective, an important consideration was given to heme oxygenase (HO). This indeed goes back to the observations made by Nath et al. (6) two decades ago demonstrating a major pathophysiological importance of HO in renal metabolism of heme proteins (6). They showed that HO activity is induced in the kidney in myohemoglobinuric AKI and such activity happened to protect the kidney. HO has two isoforms, an inducible, HO-1, and the other constitutive protein, HO-2. In follow-up studies using HO-1−/− mice, these investigators showed that the specific HO-1 isoform protects against heme protein-induced injury (8). Studies by their laboratory and others also showed the ability of HO-1 to protect against ischemic and other nephrotoxic injuries seen in AKI (1). However, all along, the role of the HO-2 was not investigated in AKI.

In looking for possible explanations for the sensitivity of the aged kidney to hemoglobin in the present study, Nath et al. (7) found that the kidney in young and old mice showed comparable induction of HO-1 mRNA following hemoglobin administration and that the aged kidney showed no induction of HO-2 mRNA, but the kidney in young mice showed a minor, but notable induction of HO-2 mRNA. This raised the possibility that HO-2 may be relevant to the resistance of young mice. Studies were then performed in relatively young mice and these studies demonstrated that the genetic deficiency of HO-2 increased the sensitivity of the kidney to hemoglobin challenge. The HO-2 isoform, like the HO-1 isoform, therefore protects against heme protein-induced AKI. Previous studies showed that HO-2 protected against streptozotocin-induced hyperglycemic kidney injury (4); nevertheless, the observations in this study are the first to report the protective role of HO-2 in any form of AKI. As such, the present studies open up new avenues for exploration in terms of HO-2, cytoprotection, and AKI.

In addition to heme-catabolizing mechanisms (HO-1 and HO-2), the present study examined how the kidney takes up hemoglobin by megalin and cubilin and whether the kidney increases its capacity for binding and taking up hemoglobin by haptoglobin/CD163, and for binding and taking up by hemopexin/CD91. The study also examined whether the kidney increases its capacity for binding iron inside cells (e.g., ferritin) or export iron out of cells (e.g., ferroportin). These studies, along with recent studies from other laboratories (10, 11), demonstrate that the injured kidney expresses increased amounts of haptoglobin and hemopexin, the proteins that are synthesized mainly by the liver. The present studies also suggest that the kidney itself is capable of synthesizing proteins that bind hemoglobin and heme and minimizing their toxicity in the kidney. Studies that assess the cellular expression and function of haptoglobin and hemopexin in the kidney after administering hemoglobin would be interesting.

Nath et al. (7) also examined in the hemoglobin-treated young and old mice kidney the renal inflammatory responses since proinflammatory cytokines are now believed to be as critical players in AKI. Prior studies from Nath’s laboratory (5) had shown the renal proinflammatory effects of heme proteins and heme. In the present study, proinflammatory cytokines were induced in the kidneys in young and old mice following hemoglobin administration, but there was an exponentially greater induction of IL-6 mRNA in the kidneys of old mice. IL-6 is a known major cytokine that plays a critical role in experimental renal ischemic damage; and plasma IL-6 is regarded as an adverse prognostic index in the hospitalized patients. The suggestion of the authors that greater induction of IL-6 contributed to hemoglobin-induced AKI in old mice is therefore reasonable. Of note, their prior studies showed that the worse ischemia-induced AKI in HO-1-deficient mice can

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be reduced by the administration of an IL-6 antibody (9), and thus it would be interesting if an IL-6 antibody can reduce the risk for hemoglobin-induced AKI in old mice. In old mice, following the treatment with hemoglobin there was a downregulation of megalin and cubulin mRNA in the kidney. These two proteins are receptors in the proximal tubule that take up albumin, light chains, hemoglobin, and other proteins. As the authors suggest, the downregulation of these receptors would result in an excessive delivery of hemoglobin to the distal nephron where hemoglobin can bind with Tamm-Horsfall protein to form casts. Thus the disadvantage of this receptor downregulation of megalin is impairment of the metabolism of heme proteins by the proximal nephron while at the same time worsening the risk for cast formation and tubular obstruction in the distal nephron. The kidneys in young mice, which show resistance to heme proteins, did not show this downregulation of megalin/cubulin, or formation of tubular casts. Downregulation of megalin/cubulin may be a unique mechanism for the formation of tubular casts in heme protein-induced nephropathies, besides the well-known capacity of heme proteins to chemically interact with Tamm-Horsfall proteins. It is tempting to speculate whether such downregulation may also apply to the abundant cast formation as occurs in “myeloma kidney,” where large quantities of light chains get to the distal nephron and form casts following interaction with Tamm-Horsfall protein.

Finally, age increases the risk for AKI but also the risk for chronic kidney disease progressing from AKI. In the present studies, heme proteins induced major genes that cause chronic inflammation in the kidneys of both young and old mice. Such gene expression in the aged kidney may be tied to the acute kidney damage that was caused by hemoglobin in the old mice. However, no such linkage can be made to this gene expression profile in young mice since this group did not show AKI following administration of hemoglobin. Thus hemoglobin can induce fibrogenic genes in the kidney without acutely damaging the kidney, and these findings may shed light on why chronic tubulointerstitial disease occurs with hematuric glomerulonephritides. Studies of interest include whether CKD occurs in old and young mice after the administration of heme proteins. As the authors suggest, the downregulation of these two proteins in the proximal tubule would result in an excessive delivery of hemoglobin to the distal nephron where hemoglobin can bind with Tamm-Horsfall protein to form casts. Thus the disadvantage of this receptor downregulation of megalin is impairment of the metabolism of heme proteins by the proximal nephron while at the same time worsening the risk for cast formation and tubular obstruction in the distal nephron. The kidneys in young mice, which show resistance to heme proteins, did not show this downregulation of megalin/cubulin, or formation of tubular casts. Downregulation of megalin/cubulin may be a unique mechanism for the formation of tubular casts in heme protein-induced nephropathies, besides the well-known capacity of heme proteins to chemically interact with Tamm-Horsfall proteins. It is tempting to speculate whether such downregulation may also apply to the abundant cast formation as occurs in “myeloma kidney,” where large quantities of light chains get to the distal nephron and form casts following interaction with Tamm-Horsfall protein.

To conclude, the present studies reflect a continuum of the long line of work that Nath’s laboratory began two decades ago in regard to heme protein-induced renal injury and how the kidney handles such an injurious assault. This study is meritorious since it alludes to the complex renal behavior to heme proteins including increased haptoglobin and hemopexin expression and the role of HO-2 in protecting against heme proteins; and last sensitivity of the aged kidney to heme proteins would likely be due to the remarkable induction of an important inflammatory cytokine, IL-6.

**REFERENCES**


