Basic science research into the underlying mechanisms of acute kidney injury (AKI) poses unique challenges, making it difficult to identify promising new targets for prevention and treatment. This month, The Journal of Clinical Investigation presents three new and unique basic science studies exploring differing mechanisms of AKI and ischemia-reperfusion injury (IRI)—each of which identifies a potentially useful new therapeutic target. “There is increasing awareness that acute kidney injury is both a major source of immediate morbidity and mortality and has a long-term impact on the development of chronic kidney disease,” said Raymond Harris, MD, FASN, President of the American Society of Nephrology. “Unfortunately, we still lack effective therapies to prevent or treat AKI. Therefore, it is encouraging that these three studies provide important new insights into the pathogenesis and offer potential avenues for prevention and treatment of AKI.”

Possible protective effect of vagal nerve stimulation

Previous research has suggested that ultrasound preconditioning of adrenergic neurons innervating the spleen has an anti-inflammatory effect—including protection against severe sepsis-induced AKI in a mouse model. Those studies identified the cholinergic anti-inflammatory pathway (CAP) as the central mechanism of protection.

In a new study, Tsuyoshi Inoue, MD, PhD, Chikara Abe, MD, and colleagues at the University of Virginia School of Medicine in Charlottesville sought to build on that knowledge by testing whether similar protective effects could be induced by ultrasound stimulation of the vagus nerve. In their mouse model, vagal nerve stimulation (VNS) ameliorated renal IRI via the same CAP activated by ultrasound. The findings included evidence that vagal efferents were the common pathway activating the CAP. The results highlight the importance of neuroimmunomodulatory mechanisms of AKI—for example, the “inter-organ crosstalk” by which injury to one kidney affects the response of the other kidney. “In the setting of multiorgan failure, such neural mechanisms are likely to be even more important,” writes Simon J. Atkinson, PhD, Vice Chancellor of Research at Indiana University–Purdue University, Indianapolis, in an accompanying commentary.

Climate Change May Contribute to Rising Rates of Chronic Kidney Disease of Unknown Origin

By Tracy Hampton

Chronic, severe dehydration linked to working in hot, humid climates for long hours may be accelerating rates of chronic kidney disease (CKD). Research published in the Clinical Journal of the American Society of Nephrology (CJASN) suggests that a condition called heat stress nephropathy may represent a disease of neglected populations, but one that may emerge as a major cause of poor kidney health as the climate continues to change (Glasser J, et al. Clin J Am Soc Nephrol. doi: 10.2215/CJN.13841215 [published online May 5, 2016]).

Over the next century, climate change and resulting water shortages are likely to affect a wide variety of health issues related to dehydration and heat stress—with risks increasing for cognitive dysfunction, malnutrition, water-borne infectious diseases, CKD, and other conditions. Some health situations, such as a great geographic spread of tropical and infectious diseases, may be more noticeable than gradual changes such as incremental increases in pollen counts that could lead to longer allergy seasons and worse asthma cases.
AKI
Continued from page 1

ny commentary. “This is a relatively neglected aspect of AKI and one that, as this new work clearly demonstrates, deserves much more attention.”

Dr. Atkinson said the findings of VNS and ultrasound show promise as a “practical preventative clinical strategy” for AKI—although, unfortunately, likely not for treatment of AKI that has already started to progress. “Given the risk and benefit profile of this strategy, one could imagine this approach being employed widely in critical care settings to reduce the risk of the serious consequences of AKI,” he said.

Drs. Inoue and Abe and colleagues note that VNS is already clinically used for treatment of drug-resistant epilepsy and depression, and is being studied for use in inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease. They predict that future studies will inform the use of therapeutic ultrasound, as a less-invasive alternative to VNS, to prevent acute injury to the kidneys as well as other organs.

Estrogen and sugar blockade as potential AKI targets

Two additional papers provide evidence of other novel mechanisms and possible therapeutic targets for AKI and IRI. Wuding Zhou, MD, PhD, and Steven H. Sacks, MD, PhD, of King’s College London led research on the contribution of C-type lectin collectin-11 (CL-11), a recently described innate immune factor, in the development of AKI. In a mouse model of ischemic injury, they found that CL-11 interacts with the stress-induced ligand L-fucose, triggering renal epithelial cell injury.

The findings clearly showed that the proximal tubule cell was the source of CL-11 responsible for mediating postischemic renal injury. The researchers also found that CL-11 binding to targeted epithelial cells was easily blocked by soluble monosaccharide inhibitors—suggesting a “physiological control mechanism that merits further exploration and exploitation” of CL-11 as a therapeutic target for hypoxic renal injury. Drs. Zhou and Sacks and colleagues add, “The broad expression of CL-11 and its putative ligands makes it possible that CL-11 operates on a wider scale, promoting inflammation and immunity in other organs and conditions.”

David D. Aufhauser, Jr., MD, and Zhonglin Wang, MD, of the University of Pennsylvania performed a study to explore the previous finding of improved recovery from IRI in females compared to males. In a mouse model of renal ischemia, the researchers found that tolerance of IRI was “profoundly increased” in females versus males. They also noted an “intermediate phenotype” of IRI tolerance after neutering of either sex.

Further experiments found that renal IRI was greater in female estrogen receptor-α knockout mice, as well as a protective effect of supplemental estrogen against AKI as well, according to an accompanying editorial by Dr. Sanjeev Noel and colleagues of Johns Hopkins University.

Coronary artery bypass graft surgery and other scenarios associated with a high risk of AKI “are excellent opportunities to examine the role of sex-specific differences in IRI and determine whether estrogen therapy can be beneficial toward protecting the kidney,” they write.

“We demonstrated that both donor and recipient hormonal milieu contribute to renal IRI tolerance,” the researchers write. “Recipient effects are dominant in human transplant outcomes, while donor effects appear somewhat stronger in mice.”

Obviously, more research will be needed to explore the clinical ramifications of the findings. But for now, Drs. Aufhauser and Wang and coauthors conclude, “[O]ur results demonstrate that sex affects renal IRI tolerance in mice and humans and indicate that estrogen administration has potential as a therapeutic intervention to clinically improve ischemia tolerance.”

If the protective effects of estrogen are supported by further studies, there may be important implications for protecting against AKI as well, according to an accompanying editorial by Dr. Sanjeev Noel and colleagues of Johns Hopkins University.

Coronary artery bypass graft surgery and other scenarios associated with a high risk of AKI “are excellent opportunities to examine the role of sex-specific differences in IRI and determine whether estrogen therapy can be beneficial toward protecting the kidney,” they write.

Have you checked out the ASN Communities yet?

Connect with colleagues. Share knowledge and resources.
Discuss issues that matter to you.

The ASN Communities site allows ASN members from around the world to connect online, join discussions, and share knowledge and resources. Members can get advice on issues they face in daily practice or research, share ideas, and provide input to ASN.

Kidney professionals from across the globe are engaged and interacting with professionals at all levels. PhD basic researchers, academics, practicing nephrologists, and many more have found a home in the ASN Communities.

Visit community.asn-online.org to join the conversation.