A wandering path toward prevention for acute kidney injury

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Acute kidney injury: challenges for therapy development
Acute kidney injury (AKI) is a common cause of hospital-related mortality; therefore, strategies to either prevent or treat this complication are of great interest. In this issue of the JCI, Inoue, Abe, and colleagues have uncovered a targetable neuroimmunomodulatory mechanism that protects mice from ischemia-reperfusion injury (IRI) and subsequent AKI. Specifically, the authors demonstrate that vagus nerve stimulation (VNS) activates the cholinergic antiinflammatory pathway (CAP), resulting in activation of antiinflammatory effects via α7 nicotinic acetylcholine receptor–expressing splenic macrophages. Together, the results of this study have potential clinical implications in the prevention of AKI in at-risk individuals.

Conflict of interest: S.J. Atkinson is a coinventor on patent applications related to the use of hydrodynamic fluid delivery for treatment of kidney injury.


Vagus nerve stimulation–mediated protection from IRI
While these observations are promising, questions remain as to how best to both...
extend these findings to a therapeutic intervention that could be implemented in clinical practice and to uncover the precise neural mechanisms involved. Vagus nerve stimulation (VNS), in which a pattern of electrical stimulation is delivered to the vagus nerve from a pulse generator implanted in the chest (with noninvasive transcutaneous devices in development), is approved for treatment of epilepsy and depression (10). Studies in animal models to evaluate the use of VNS in brain and heart IRI, for example, suggest that this strategy is capable of activating the CAP (7). In this issue, Inoue, Abe, and colleagues point to the underappreciated importance of neuroimmunomodulatory mechanisms in AKI. Indeed, the AKI literature is replete with evidence that interorgan effects are important for disease development, even in simplistic models of AKI, such as the commonly employed renal artery clamp IRI model (3). This interorgan crosstalk is exemplified by the way that injury to one kidney profoundly affects the response of the other, contralateral kidney (see, for example, ref. 12). Interorgan trafficking of immune cells and dissemination of inflammatory cytokines are surely responsible for many of these effects, but the present study by Inoue, Abe et al. again reinforces the view that neural mechanisms are also likely to contribute in important ways to this phenomenon (5). Indeed, in the course of their study, the authors replicated the previous observation (13) that renal sympathetic denervation profoundly decreases injury in one model of IRI. In the setting of multiorgan failure, such neural mechanisms are likely to be even more important. This is a relatively neglected aspect of AKI and one that, as this new work clearly demonstrates, deserves much more attention.

Conclusions and future directions
The effectiveness of VNS and ultrasound in mouse models is promising for further development of a practical preventative clinical strategy to reduce the incidence of AKI. Unfortunately, the ability of such an approach to treat AKI that has already started to progress is not a likely outcome, as the protective effect of neuroimmunomodulation only developed after a significant delay — VNS was effective at attenuating AKI when delivered at 24 hours but not at 2 hours prior to injury (5). Therefore, the most likely clinical use for this approach would be as a prophylactic measure in situations where the patient is at high risk of developing AKI. In favor of neuroimmunomodulation as a preventative strategy is that the treatment itself, VNS or ultrasound (the ultrasound modality used in these studies generates little heat in the target tissues), is either noninvasive or minimally invasive, and there is minimal risk from either procedure itself. 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, analogously to the provision of vaccines as low-risk preventative measures against infectious diseases.
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