Uncovering the pathway of sepsis-induced renal tubular dysfunction.

Focus on “Basolateral LPS inhibits NHE3 and HCO$_3^-$ absorption through TLR4/MyD88-dependent ERK activation in medullary thick ascending limb”

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Submitted 20 September 2011; accepted in final form 20 September 2011

SEPSIS is the body’s systemic response to severe infection, and it is associated with multiple organ dysfunction (e.g., neurological, pulmonary and renal). Indeed, severe sepsis affects millions of patients each year with a mortality rate between 30% and 40% (2).

During sepsis, arterial blood pressure drops significantly leading to sepsis-induced hypotension in septic shock. This drop in blood pressure is due to the activation of a complex hemodynamic response, which, in the kidney, leads to vasoconstriction and low renal blood flow followed by renal tissue hypoxia, ischemia, and rapid loss of kidney function (10).

The poor delivery of oxygen to the kidney greatly diminishes its aerobic metabolism, and the kidney’s decrease in blood flow renders it unable to clear the body of the accumulation of organic acids produced by the enhanced anaerobic metabolic processes. Proton accumulation from organic acids in combination with the kidney’s inability to reabsorb bicarbonate, due to sepsis-induced acute kidney injury (AKI), leads to prolonged metabolic acidosis (7).

Despite the association between the onset of metabolic acidosis and adverse clinical outcomes in critically ill septic patients, effective treatments of this severe acid-base disturbance remain elusive (7). Understanding the cellular mechanisms activated by sepsis to alter the acid-base balance in the kidney would provide useful targets to manipulate and, hence, to affect our ability of monitoring acid-base disturbance specifically during sepsis.

The kidney plays a key role in regulation of the extracellular fluid pH, hence, in the acid-base homeostasis, by reclaiming the bicarbonate filtered at the glomerulus and generating new bicarbonate by secreting protons into the urine. The Na$^+$/H$^+$ exchanger isoform 3 (NHE3) is a major player in bicarbonate absorption and proton excretion in the renal tubule. NHE3 is part of the NHE protein family of ubiquitous transmembrane proteins that mediate the exchange of sodium for proton across the lipid bilayer (1). In the kidney, NHE3 is expressed mainly at the apical membrane of the proximal tubule and the thick ascending limb, where it mediates 70–85% and 10–20% of bicarbonate absorption, respectively (Fig. 1). Accordingly, target disruption of NHE3 in mice causes hypotension, hypo-volemia, and metabolic acidosis (11).

Injection of lipopolysaccharides (LPS), a bacterial cell wall molecule, provokes severe sepsis in experimental animals and causes a time-dependent pronounced hypotension, tachycardia, and AKI. Fractional sodium excretion increases after LPS injection, which is probably due to reduced protein expression of several sodium transporters; hence, in a decrease in sodium reabsorption. In particular, NHE3 protein expression has been shown to be strongly reduced by LPS treatment (9).

Of interest, low-dose LPS, which provokes a release of pro-inflammatory cytokines in the absence of systemic hypotension, still reduces NHE3 protein expression (9). These findings raise the following questions: 1) What are the signaling pathways activated by LPS to specifically target NHE3 function in sepsis? 2) Is reduced abundance of NHE3 after LPS treatment merely the product of renal tubule damage or a sign of renal tubule energy conservation? A detailed characterization of the signaling cascades activated by LPS to regulate NHE3 and bicarbonate reabsorption shall shed some light on the understanding of the processes that are activated during sepsis to damage or to protect kidney function.

Indeed, in previous in vitro studies, Good et al. (5) have demonstrated that LPS reduces bicarbonate reabsorption in the medullary thick ascending limb (MTAL) through the activation of distinct Toll-like receptor (TLR4, single transmembrane cell-surface receptors that have a key role in the innate immune system)-dependent signaling pathways in the basolateral and apical membranes. In this issue of the Am J Physiol-Cell Physiol, Watts et al. (13) aimed to further investigate the mechanisms whereby basolateral LPS impairs bicarbonate reabsorption in MTAL. The authors found that LPS specifically triggers the TLR4/myeloid differentiation factor 88 (MyD88)/mitogen-activated protein kinase (MEK)/extracellular-signal regulated kinase (ERK) signal transduction pathway and that NHE3 is a direct downstream target of LPS. Moreover, they showed that the LPS-induced inhibition of NHE3 is due to a reduction in the $V_{\text{max}}$ of the exchanger and does not modify the affinity of the transporter for intracellular protons.

The ERK has been extensively implicated in mediating the pathophysiological consequences of sepsis. However, the role of the ERK signal transduction pathway in sepsis-induced renal tubular dysfunction has not been fully established. The study by Watts et al. (13) provided convincing functional and molecular evidence that the ERK pathway links LPS-induced TLR4 signaling to inhibition of ion transport, including: 1) inhibition of bicarbonate reabsorption was eliminated by the specific MEK/ERK inhibitors U0126 and PD98059; 2) LPS induced a rapid and sustained increase in the ratio of pERK to...
total ERK in microdissected MTALs; and 3) inhibition of NHE3 activity by LPS was abolished by MEK/ERK inhibitors. From these observations, Watts et al. have proposed that components of the TLR4-ERK signaling pathway may serve as a potential therapeutic targets to treat or prevent sepsis-induced impairment of tubular function.

As discussed by Watts et al. (13), the mechanisms by which ERK regulates NHE3 activity in the renal tubule are yet to be defined. Indeed, in the proximal tubule, activation of ERK has been shown to be involved in both stimulation (12) and inhibition (3, 6) of NHE3 activity. Tsuganezawa et al. (12) have shown that the ERK pathway is required for acid activation of NHE3 in OKP cells. In contrast, studies with the pharmacological inhibitors PD98059 (6) and U0126 (3) revealed that cAMP-dependent inhibition of NHE3 activity is partially dependent on activation of the MEK/ERK signaling cascade in cultured renal proximal tubule cells. Noteworthy, by means of stationary in vivo microperfusion, the Malnic laboratory has found that addition of U0126 to proximal tubule luminal fluid from an otherwise untreated rat significantly decreases bicarbonate efflux (1.31 ± 0.10 vs. 2.08 ± 0.11 nmol·cm⁻²·s⁻¹ in control, P < 0.0001) suggesting that the ERK pathway plays a tonic role in stimulating NHE3-mediated bicarbonate reabsorption in this segment of the nephron (Queiroz-Leite G. D. and Malnic G., unpublished data). Furthermore, given the distinct pattern of proteins that physically and/or functionally interact with NHE3 in the proximal tubule vs. MTALs, the mechanisms by which ERK modulates NHE3 are, most likely, nephron segment specific.

Taking into account the complexity of the ERK pathway combined with the fact that this cascade may elicit both protective and detrimental effects, it seems, at first glance, implausible to attempt to inhibit this pathway in a clinical setting. This question was elegantly addressed by the authors: “The fact that ERK pathways activated by different stimuli may result in different outcomes with respect to NHE3 activity (or other cellular responses) does not preclude the ERK pathway as a potential target for therapeutic intervention. Rather, it emphasizes the need for future work to understand the molecular components responsible for the specificity of the ERK signaling in response to different stimuli”. The results from these further studies are eagerly awaited.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: F.D.S. prepared figures; F.D.S. and A.C.C.G. drafted manuscript; F.D.S. and A.C.C.G. edited and revised manuscript; F.D.S. and A.C.C.G. approved final version of manuscript.

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