Subclinical kidney injury incites endotoxin hyperresponsiveness

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GENTAMICIN, an AMINOGLYCOSIDE discovered in 1963 from micromonospora, is one of the most commonly used antibiotics against Gram-negative infections. Aminoglycosides achieve bacterial killing by binding to bacterial ribosomes, causing blockade of protein synthesis through failure of initiation and misreading of messenger RNA. The effectiveness of these antibiotics is emphasized by the following factors: 1) efficient bactericidal nature (fast and concentration-dependent killing), 2) postantibiotic effect (continued suppression of bacterial growth when concentrations fall below MIC), 3) low development rate of resistance to the antibiotic, and 4) synergism when combined with β-lactam antibiotics (8). Due to the aforementioned factors, gentamicin is considered a breakthrough in the treatment of Gram-negative sepsis and remains one of the most frequently used aminoglycosides in clinical practice. However, the dose-dependent effects of gentamicin on the kidney resulting in acute renal failure (15–20% of all cases) have restricted its use (2, 9).

Several mechanisms have been suggested to account for gentamicin-induced acute renal failure (2, 9). These include generation of reactive oxygen and nitrogen species (17, 21), release of inflammatory components from dying bacteria, and inhibition of protein synthesis (3). Gentamicin accumulates in the kidneys of both experimental animals (6, 12) and humans (1, 5, 11) and is taken up selectively by proximal tubular cells of the nephron (11) by high-affinity binding to megalin (13). This feature has helped establish the use of gentamicin as a model for segment-specific injury to the proximal tubule. Besides nephrotoxicity, gentamicin is also known to cause ototoxicity, which results from transient high peak concentrations in the serum and inner ear (18).

In the course of treatment for Gram-negative sepsis with gentamicin or other antimicrobial agents, lipopolysaccharide (LPS) and components of the bacterial cell wall are released and these can induce inflammatory cascades. This phenomenon known as the Jarisch-Herxheimer reaction was first described in syphilitic patients treated with mercury. Studies have shown increased levels of LPS following antibiotic treatment of infections in clinical (10) and experimental settings (7, 14, 19). LPS, in the presence of infection, trauma, ischemia, or nephrotoxins, induces synthesis of cytokines/chemokines such as TNF-α, interleukin-10 (IL-10), and monocyte chemotactic protein-1 (MCP-1) (4, 20). The presence of Gram-negative sepsis also predisposes to increased susceptibility to acute renal failure from ischemia or nephrotoxins (22, 27).

In a paper in the present issue of the American Journal of Physiology-Renal Physiology, Zager’s laboratory (23) has explored the risk of gentamicin treatment on the potentiation of endotoxin-driven inflammatory responses. Previous studies from his laboratory had explored this link under settings of urinary tract obstruction, renal ischemia-reperfusion, and cisplatin nephrotoxicity, where it was observed that overt kidney injury resulted in hyperresponsiveness to LPS (24–26). In this most recent work, the author sought to examine whether selective proximal tubule injury alone could heighten this response and whether this state of hyperresponsiveness could be expressed in the absence of obvious tubular injury and renal failure. Gentamicin was chosen due to its inherent nature of selective uptake by the proximal tubular cells, and a low subclinical dose of the agent that did not inflict structural or functional renal damage was utilized. LPS was administered at 0, 24, or 72 h after gentamicin treatment, and cytokine profiles were measured in the kidney, liver, spleen, and serum. Even a single subclinical dose of gentamicin followed by LPS administration was capable of dramatically altering the cytokine profiles for TNF-α and MCP-1 in the kidney. This response was not restricted to the kidney alone, where gentamicin is preferentially concentrated, but was also observed in extrarenal organs such as the liver. This hyperresponsiveness was observed when mice were pretreated with gentamicin 1 or 3 days before LPS administration or when both the agents were simultaneously administered. The findings also highlight that gentamicin, known to inhibit protein synthesis, perhaps preferentially upregulates transcription of inflammatory genes, thereby producing the expected outcome. Interestingly, levels of the anti-inflammatory cytokine IL-10 were also upregulated in the kidney. It is possible that this may represent an adaptive mechanism to balance the otherwise increased proinflammatory response.

The priming effect of LPS is not restricted to subclinical gentamicin-induced proximal tubular injury but also extends to other nephrotoxins. A recent study by Ramesh and colleagues (15) has reported similar findings following a nonnephrotoxic dose of cisplatin (15). Low-dose cisplatin (10 mg/kg) had no effect on renal function but sensitized the kidney to subsequent LPS exposure, resulting in increased intrarenal production of TNF-α, worse renal function, and increased mortality in mice. Using TLR-4-deficient and TNF-α-deficient mice, these authors showed that the priming effect of LPS following cisplatin was dependent mainly on TLR-4 signaling and partially dependent on TNF-α.

The findings of Zager (23) are germane to our clinical practice, where the dose of gentamicin is usually decreased in patients with kidney disease and reduced renal function. The results showing that even low doses of gentamicin can prime not only the kidney but also extrarenal organs to endotoxin-mediated hyperresponsiveness provide an important and relevant concept that will impact the use of gentamicin in the treatment of Gram-negative sepsis. It would be of great interest to evaluate whether the newly described nonnephrotoxic gentamicin congeners (that retain bactericidal properties with no
significant nephrotoxicity) (16) exhibit similar effects in terms of endotoxin hyperresponsiveness.

REFERENCES