Regulation of AQP Water Channels: Role of Oxidative Stress and Inflammation

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Renal tubulo-interstitial inflammation is frequently associated with polyuria and urine concentration defects. This led us to investigate the effects of the major pro-inflammatory and oxidative stress pathway on aquaporin expression by the collecting duct. We found that gentamicin and cisplatin treatment increased serum creatinine levels along with urinary concentration defect. Accordingly, the expression of AQP1, Na, K-ATPase α1 and NHE3 was decreased in the kidney. Immunoperoxidase microscopy of AQP1 and NHE3 also showed a pronounced decrease of its labeling in the proximal tubule. Moreover, paricalcitol prevented the dysregulation of these transporters and improved the renal function. The molecular mechanisms, by which the expression of renal sodium transporters and AQP1 water channel is decreased in the kidneys in drug-induced kidney injury, are unknown. The expression of NHE3 and AQP1 examined by Western blot and immunohistochemistry was reduced in the proximal tubule, and tubular dilatation, blebs and denuded cells were seen in the proximal tubules from the genatmicin and cisplatin treated kidneys. This raises a possibility that genatmicin and cisplatin treatment causes generalized cell dysfunction and protein mal-metabolism associated with structural changes in the proximal tubule, which may cause down-regulation of NHE3 and AQP1. Other secondary mechanisms, however, may also contribute to the decreased expression of NHE3 and AQP1. Recent study demonstrated that lipopolysaccharide (LPS)-induced inflammation down-regulated the expression of renal sodium transporters and AQP water channels. In addition, in cortical collecting duct cells exogeneous injection of TNF-α, IL-1β or IFN-γ also decreased renal tubular function and inhibited the expression of renal sodium transporters. We showed that the expression of renal pro-inflammatory markers such as TNF-α, IL-1β, and IFN-γ was increased in drug-induced kidney injury, which was reversed by paricalcitol. These findings suggest that the restoration of AQP1 and sodium transporters by paricalcitol may in part be ascribed to quenching inflammatory responses. Inflammatory cells release pro-inflammatory chemokines, thereby leading to the formation of a vicious self-accumulation circle. Not surprisingly, decline of renal function in CKD often correlates to the extent of inflammation. We demonstrated that genatmicin and cisplatin-treated rats displayed a marked increase in monocyte/macrophage infilatration into the renal cortex/medulla, as indicated by the large number of ED-1 positive cells in the interstitium. These findings are consistent with previous observations which demonstrated that genatmicin and cisplatin can cause an increase in monocyte/macrophage populations in the kidney. Drug increased expression of pro-inflammatory markers such as TNF-α, IL-1β, IFN-γ and iNOS. These inflammatory molecules participate in the pathogenesis of tubulointerstitial impairment via the promotion of leukocyte attraction and adhesion to inflamed renal tubular cells. The expression of cell surface adhesion molecules such as MCP-1, ICAM-1 and VCAM-1, which are highly specific chemotactic factors for macrophages, was increased in GM-treated kidney. These findings indicate the inflammatory process has a significant

role in the pathogenesis of GM-induced renal injury. Furthermore, we showed paricalcitol significantly reduced the infiltration of ED-1 expressing macrophages in the kidney and decreased renal expression of pro-inflammatory cytokines and cell surface adhesion molecules induced by genatmicin and cisplatin. NF-κB is thought to be a key transcription factor underlying renal inflammatory process by regulating gene expression of cytokines, chemokines, and adhesion molecules in progressive renal diseases. In unilateral ureteral obstruction (UUO) and GM rat model, NF-κB is activated followed by UUO or GM administration, and blockade of NF-κB activation reduced apoptosis and interstitial fibrosis. NF-κB is released from an inhibitory subunit IκB and translocates into the nucleus, where it promotes the transcriptional activation of target genes. We found that the expression of nuclear p65 subunits of NF-κB was increased after GM treatment in HK-2 cells, which suggest that GM induced NF-κB activation and translocation via IκB-α degradation. Importantly, paricalcitol prevented the NF-κB activation induced by GM. Recent experiment also suggests that paricalctiol is able to repress the NF-κB-mediated gene transcription in inflamed renal tubular epithelium. Hence, it seems reasonable to assume that therapeutic drugs which target on anti-inflammatory and anti-oxidant action may exert its immunomodulatory action in acute kidney injury through inhibiting NF-κB signaling pathway.

On the other hand, it has been known that reactive oxygen species (ROS) are powerful mediators of renal endothelial and tubular cell injury, and hence, antioxidants may be potential candidates for prevention or treatment of ischemia/reperfusion (I/R)-induced renal injury. α-Lipoic acid (α-LA) has been known as a potent antioxidant, of which anti-oxidant effects are attributed to direct radical scavenging and metal chelation. We have demonstrated the downregulation of AQP and major sodium transporters, along with impaired urinary concentrating ability and renal sodium handling in I/R-induced acute kidney injury. We further demonstrated that α-LA treatment prevented the dysregulation of AQP and sodium transporters, and reserved the urinary concentration ability and tubular sodium reabsorption capability despite the I/R-injury.

Enhanced ROS production and tubulointerstitial inflammation in the kidney resulted in downregulation of AQP and major sodium transporters in acute kidney injury, coinciding with the impairment of urinary concentration and decreased tubular reabsorption of filtered sodium. Anti-oxindant and anti-iflammatory treatment has a protective effect against renal injury, such as normalizing the renal hemodynamics, urinary concentration ability and excrection of sodium, along with the expression of AQP and sodium transporters.