Effects of salt intake on the intracellular signal transduction of TGF-β in anti-thymocyte serum (ATS) nephritis

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Summary

Increased TGF-β expression has been shown to be involved in deterioration of renal function resulted from pathologic matrix accumulation in glomerulonephritis. This study was conducted to explore the effects of salt intake on the intracellular TGF-β signal transduction composed of the receptor-regulated Smads 2 and 3, the common mediator Smad4, and the inhibitory Smad6 in ATS nephritis. Rats were fed with low salt diet (0.03% NaCl chow; LS), normal salt diet (0.39% NaCl chow; NS), or high salt diet (0.39% NaCl chow and 1% NaCl as drinking water; HS). Furosemide 2 mg/kg was injected 7 days before ATS injection in LS and deoxycorticosterone acetate 10 mg/kg 14 and 7 days before ATS injection in HS. We studied the levels of blood pressure, proteinuria, renal lesions, TGF-β1 (ELISA) and Smad2 (Western blot) in isolated glomeruli, and immunohistochemical staining for Smads 3, 4, and 6 in kidney tissues. The mean arterial blood pressure levels did not differ significantly among the groups. The levels of proteinuria, proliferative glomerular lesions with mesangial matrix accumulation, and glomerular TGF-β1 expression increased transiently, peaked at day 7, in LS and NS, and were less severe in LS than NS. In contrast, they were markedly severe in HS. In NS glomeruli at day 7, Smad2 decreased remarkably, Smad3 decreased in the nuclei and increased in the cytoplasm, Smad4 did not change in the nuclei but increased in the cytoplasm, and Smad6 increased in the cytoplasm. The marked decrease of glomerular Smad2 was also noted in LS and HS. The increase of cytoplasmic Smad4 at day 7 was slight in LC, while the decrease of Smad3 was remarkable and the increase of Smad6 was slight in the glomeruli with severe lesions in HS at day 7. These data suggest that the intracellular TGF-β signal transduction through Smad2 followed by the proteolysis through the ubiquitin-proteasome pathway is predominant in ATS nephritic glomeruli and the increase of Smad3-mediated signaling and the decrease of Smad6-mediated signal inhibition could be involved in the aggravation and prolongation of ATS nephritis in HS.