Pathophysiological role of hypertonic stress by salt loading in the kidney

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Summary

Na^+/*myo*-inositol cotransporter (SMIT) was a major osmolyte transporter that is regulated by extracellular osmolarity. We examined the expression of SMIT in partial nephrectomized rats in order to assess the change in local osmolarity following reduction of renal mass. Four weeks after 5/6 nephrectomy, the rats were compared to sham-operated control animals. In situ hybridization revealed that signals for the transporter mRNA were markedly reduced in the inner medulla of the remnant kidney. In contrast, these signals in the outer medulla as well as cortex increased following nephrectomy. Microscopic examination revealed that the signals in the thick ascending limbs of Henle (TAL) as well as macula densa cells were significantly increased. The signals in this segment were reduced by furosemide administration. The increased expression in NX rats appears to reflect the increased NaCl transport and high local osmolarity in this segment.

Hypertonicity is known to modulate the expression of some genes and the action of several cytokines. We next evaluated whether hypertonicity would increase the expression and/or activity of transforming growth factor-ß (TGF-ß) in NRK cells. The bioassay for TGF-ß showed that mature TGF-ß activity was significantly increased when the cells were cultured in a hypertonic medium (500 mOsm/kg). In contrast, total TGF-ß activity and TGF-ß mRNA abundance did not change significantly, suggesting that hypertonicity activated TGF-ß without affecting the synthesis of TGF-ß. To determine whether collagen synthesis was increased by hypertonicity, we examined [3H] proline incorporation into NRK cells cultured in hypertonic medium. Proline incorporation increased in an osmolality-dependent manner. Furthermore, anti-TGF-ß antibody prevented the increase in proline incorporation induced by hypertonicity. These results suggest that hypertonicity promotes the processing of latent TGF-ß to the biologically active form, resulting in the stimulation of collagen synthesis in NRK cells.

To examine possible role of local hypertonicity in renal fibrosis, we investigated the expression of TGF-ß and fibronectin in the remnat kidney. In situ hybridization revealed that signals for TGF-ß mRNA were markedly increased in the outer medulla and cortex following nephrectomy. Microscopic examination revealed that the signals in the outer medulla were localized to the interstitial cells as well as the TAL cells. The expression of fibronectin showed a similar pattern. These results suggested a possible involvement of hypertonic stress in the progression of renal diseases.