Regulation and an important role of Na^+/*myo*-inositol cotransporter in the kidney

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Summary

Myo-inositol, a major compatible osmolyte in renal medulla, is accumulated in several kinds of cells under hypertonic conditions via Na^+/*myo*-inositol cotransporter (SMIT). We have recently shown that SMIT mRNA in the thick ascending limb of Henle (TAL) was rapidly upregulated by NaCl loading and was downregulated by furosemide, suggesting that the expression is proportional to NaCl transport (J Clin Invest 96: 1195, 1995). To confirm this notion, we examined the effects of administration of acetazolamide, which inhibits NaCl reabsorption in proximal tubule, in rats. In situ hybridization for SMIT revealed that acetazolamide apparently induced SMIT mRNA in the outer medulla of the kidney as expected. We next examined the effects of inhibition of *myo*-inositol transport using an analogue of *myo*-inositol, 2-*O*, *C*-methylene-*myo*-inositol (MMI). We first characterized the inhibitory effect of MMI on *myo*-inositol transport in Madin-Darby canine kidney (MDCK) cells. The Na^+-dependent component of [^{3}H] *myo*-inositol uptake was inhibited by MMI in a concentration-dependent manner. We found decreased affinity for *myo*-inositol in the presence of MMI whereas the Vmax of the transporter did not change. Thus, MMI behaves as a competitive inhibitor of *myo*-inositol transport with a relatively high Ki value (1.6 mM). *Myo*-inositol content in hypertonic MDCK cells was markedly reduced in the presence of 5 mM MMI, but MMI itself did not accumulate in these cells. We next examined the *in vivo* effects of MMI administration on rat kidney. Intraperitoneal injection of MMI (60~80 mg/kg) caused tubular degeneration and necrosis predominantly in the outer medulla. Serum creatinine and urea nitrogen elevated significantly 16 hours after MMI administration. Immuno-histological study for Tamm-Horsfall protein (THP) revealed that degenerated tubular cells were THP-positive, indicating that they were the TAL cells. NaCl loading apparently deteriorated the tubular injury. Administration of *myo*-inositol prevented the toxic effect of MMI. Furthermore, high dose of betaine, another osmolyte in the TAL cells, partially prevented the adverse effect of MMI. We conclude that *myo*-inositol play a crucial role in the TAL regarding osmoregulation of the cells.