NaCl Sensor Mechanism of Renal Tubular Potassium Channels

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Summary

Potassium permeability of renal epithelial cells is a crucially important parameter in kidney function. An ATP-sensitive K^+ channel ROMK1 and its splice-variants ROMK2 and ROMK3 have recently been cloned from kidney and most likely represent low-conductance K_{ATP} channels of TAL, CCD and macula densa (Hebert and Wang 1997). Macula densa cells have been shown to possess high density of potassium channel of intermediate conductance, responding to the changes in extracellular Na^+ (Hurst et al. 1994). Recent studies have established the presence of both ROMK potassium channels (Xu et al. 1997) and NHE3 type Na/H antiporters (Amemiya et al. 1995). The aim of this project was to reveal a possible regulation of renal epithelial K^+ channels by Na^+.

The macroscopic ROMK1 current expressed in *Xenopus* oocytes was found to slowly inactivate upon replacement of extracellular Na^+ ions with $NMDG^+$. Maximal value of inhibition was app. 50% and could be significantly enhanced by coexpression of sodium-proton exchanger NHE3. Amiloride at 10 μM greatly changed the inhibition kinetics, suggesting that Na-dependent inhibition is mediated, at least in part, by sodium-proton antiport. Direct interaction of Na with the external entrance to the pore is not involved in the process, since the inhibition could be seen in cell-attached macropatches (pipettes contained constant NaCl) upon extracellular Na^+ or NaCl removal. In addition, single channel amplitudes and gating kinetics were the same in cell-attached single-channel recordings when pipette solution contained either NaCl or mannitol.

ROMK1 channels transiently expressed in a human embryonic kidney cell line, HEK 293, were rather insensitive to the extracellular NaCl. However, coexpression with NHE3 antiporters conferred profound Na^+ sensitivity on the channel. Upon replacing NaCl with mannitol the inhibition could be as deep as 80%.

Taken together, it is concluded that a cross-talk between ATP-sensitive K^+ channels and Na/H exchangers is likely to represent one of the mechanisms of the tubuloglomerular feedback signal transduction in kidney.