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Regulation of tight junction proteins by NaCl loading in renal tubular epithelial cells

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Objectives:

We previously reported that tight junction (TJ) proteins were altered in rat kidneys with salt-sensitive hypertension. This study was undertaken to evaluate alterations of TJ proteins in proximal tubular and collecting duct epithelial cells in response to NaCl loading.

Methods: Three different cell lines (HK-2, MDCK I, and mpkCCD) were used, and cells were exposed to additional NaCl (0 to 30 mM) for 24 h. The expression of TJ proteins were examined by immunoblot analysis, and paracellular permeability was determined using transepithelial electrical resistance (TER) and transepithelial flux rates of dextrans (4- and 70-kDa). Also, these responses were tested after transfecting small-interfering RNAs against claudins, occludin and ZO-1 in HK-2 and MDCK I cells.

Results: In HK-2 cells, NaCl loading induced a decrease in claudin-2, an increase in occludin and a decrease in TER. In MDCK I and mpkCCD cells, occludin and TER were increased by NaCl loading. Besides, ZO-1 in MDCK I cells and claudin-4 in mpkCCD cells were increased by NaCl loading. When claudin-2 was deficient in HK-2 cells, occludin increased and TER decreased. When occludin was deficient, claudin-2 decreased and TER increased. Notably, these changes were reversed by NaCl loading. In MDCK I cells, inhibition of claudin-4 was not associated with any changes in occludin, ZO-1 and TER. However, claudin-4 and TER were increased by NaCl loading. Inhibition of ZO-1 was also reversed by NaCl loading in association with an increase in 70-kDa dextran flux.

Conclusions: HK-2, MDCK I, and mpkCCD cells showed differential responses of TJ proteins and TER after NaCl loading. In both HK-2 and MDCK I cells, TJ protein knockdowns were partially reversed by NaCl loading in association with changes in paracellular permeability. We conclude that TJ proteins are regulated by NaCl loading in proximal and distal nephron, suggestive a role in salt-sensitive hypertension.