MOLECULAR PATHOPHYSIOLOGICAL STUDY OF ELECTROLYTE TRANSPORTERS IN RENAL TUBULAR CELLS

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Patients with lifestyle-related diseases such as hypertension, diabetes, and hyperlipidemia are at high risk for the pathogenesis of a life-threatening atherosclerotic disease. We think that the elucidation of the mechanism responsible for the pathogenesis can bring about the prevention and the cure of lifestyle-related diseases. We examined the regulatory mechanisms of expression and function of renal electrolyte transporters and the dysfunction of transporters in hypertension.

(1) The regulatory mechanism of trascellular and paracellular Mg^{2+} transport

TRPM6, a member of the transient receptor potential superfamily, is expressed in the apical membrane and may be involved in the reabsorption of Mg^{2+} in the distal convoluted tubule. We found that the expression of TRPM6 is up-regulated by the phosphorylation of ERK and an increase in c-fos. Cyclosporin A (CsA) is used for therapeutic purposes such as organ transplantation. However, its clinical application can have severe adverse effects including nephrotoxicity and hypomagnesemia. TRPM6 expression was decreased by CsA. We have to investigate the relation between the abnormal expression of TRPM6 and pathogenesis in future studies.

Claudin-16 is expressed in the tight junction (TJ) of the thick ascending limb of Henle and may be involved in the regulation of paracellular Mg^{2+} transport. A high-salt diet in Dahl salt-sensitive (DS) rats reduces the renal reabsorption of Mg^{2+} and develops hypertension. A high-salt diet decreased the level of serine-phosphorylated claudin-16 without affecting total amount of claudin-16. Claudin-16 was phosphorylated by protein kinase A in Madin-Darby canine kidney cells expressing FLAG-tagged claudin-16. Phosphorylated claudin-16 was distributed in the TJ and increased Mg^{2+} transport. In contrast, dephosphorylated claudin-16 was distributed in the intracellular compartment and did not increase Mg^{2+} transport. These results suggest that the dephosphorylation of claudin-16 causes the reduction of Mg^{2+} reabsorption.

(2) The regulatory mechanism and function of Na^{+}-dependent glucose transport

In proximal tubule, glucose is reabsorbed into cells by Na^{+}-dependent glucose transporter (SGLT1 and SGLT2). A high-salt diet in DS rats increased the SGLT1 activity. Heat stress increased the distribution of SGLT1 on the apical membrane and glucose uptake in renal epithelial cells. The activation of SGLT1 was involved in the recovery of tight junctional integrity. We suggest that glucose uptake is increased by stress injury in order to recover from cellular damage. We hope the clinical application of a novel SGLT1 inhibitor because the activation of SGLT1 may develop not only diabetes but also hypertension.