No. 1929

The Molecular Mechanism of Na^+ sensing and Feedback Regulation of Glomerular Filtration in the Kidney

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Summary

Kidney plays important roles in the regulation of body fluid volume and blood pressure by reabsorption of electrolytes (Na^+, K^+, etc.) from filtered fluids through glomerular filtration units. Filtered nutrient such as glucose, and amino acids, are almost completely reabsorbed in the proximal tubules, and are backed to the circulation. On the other hand, 60 % of filtered Na^+ are reabsorbed in the proximal tubules for the Na^+ dependent reabsorption of the nutrients, and remaining Na^+ was reabsorbed through the distal nephron including thick ascending limb of Henle (TALH), and collecting duct for the water reabsorption. The renal macula densa (MD) cells, which are packed specialized cells lining the wall of the TALH at the transition to the distal convoluted tubule. MD cells sense the luminal concentration of NaCl in TALH, and mediate the feedback regulation of glomerular filtration, so-called “tubule-glomerular feedback”. MD cells sense the luminal concentration of NaCl in TALH, and release several kinds of signaling molecules including prostaglandins (PGs) and adenosine to regulate the glomerular hemodynamics by the vasodilation or vasoconstriction of afferent arterioles. Recently, we found that MRP4 (Multidrug Resistance Protein 4) as a candidate transporter for PG release in MD cells. In the present study, we examined physiological roles of MRP4 in the regulation of PG release from renal MD cells by using MRP4 knockout mice. Urinary and plasma concentrations of electrolytes, creatinine, and fractional excretion of electrolytes were not significantly different between wild type mice (WT) and $MRP4^{(-/-)}$ mice during the experimental period. However, $MRP4^{(-/-)}$ mice displayed hypotensive phenotype compared with WT mice. $MRP4^{(-/-)}$ mice also exhibited the lower level of PGE_2 production in the renal cortex, possibly due to the significantly decreased COX-2 expression level in the cortex of $MRP4^{(-/-)}$ mice. Our findings suggest that MRP4 plays an important role in the control of renal function, although it seems to be responsible for the regulation of PGE_2 production rather than PGE_2 release from MD cells.