No. 0639

New Therapeutic Approach for Hypertension through Regulation of Na^+ Balance

Masayuki Tanemoto, Sadayoshi Ito

Division of Nephrology, Hypertension & Endocrinology
Department of Medicine, Tohoku University Hospital

Summary

【Back ground and objectives】Hypertension, the most common disorder in industrialized societies and an independent risk factor for end-organ damage, is one of the chief burdens of the healthcare system. The treatment of hypertension based on its pathophysiology can arrest the progression of end-organ damage, and will relieve the burden on the healthcare system. Recent genetic analysis has revealed that the Na^+ reabsorption in the distal convoluted tubules (DCT), which depends on K^+ recycling, participates in the pathogenesis of hypertension. Previously, we showed that the Kir5.1/Kir4.1 heteromer, which is an heteromeric assembly of two inwardly rectifying K^+ channels, comprises the principal pathway for the basolateral K^+ recycling in the DCT, and that two motifs in the carboxyl terminal portion of the Kir4.1 subunit regulate its functional expression. Therefore, the mechanism that recognizes these motifs is thought to be a key factor for the renal regulation of Na^+ and K^+ homeostasis. In this study, we aimed to identify the mechanism.

【Methods and Results】By using yeast two-hybrid screening, we identified a new isoform of Membrane Associate Guanylate kinase with Inverted domain structure 1 (MAGI-1a) as a scaffolding protein for the channels that comprise the basolateral K^+ recycling pathway. By using the anti-MAGI-1 antibody, which specifically recognizes MAGI-1a, we further revealed the interaction between MAGI-1a and Kir4.1 in the kidney, and the colocalization of MAGI-1a with Kir4.1 in the DCT. MAGI-1a interacted with the PSD-95/Dlg/ZO-1 (PDZ)-binding motif of Kir4.1 through its 5^{th} PDZ domain, and the phosphorylation of the motif impeded the interaction.

【Conclusions】A new splice variant of MAGI-1a plays a regulatory role in the basolateral K^+ recycling by functioning as a scaffolding protein for the K^+ channels that comprise the recycling pathway. The phosphorylation of the channels impedes the anchoring of the channels by MAGI-1a and decreases the basolateral K^+ recycling. Affecting the activity of the basolateral K^+ recycling, the pathway for channel phosphorylation could coordinate renal Na^+ and K^+ reabsorption in the DCT. These findings suggest that the phosphorylation -dependent regulation of basolateral K^+ recycling by MAGI-1a could be a new target for the treatment of hypertension and hyperkalemia.