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Mechanisms of Salt-Sensitive Hypertension in Chronic Kidney Disease Caused by WNK Signal Regulation by Immune Mechanism

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Summary

The inappropriate over-activation of with-no-lysine kinase(WNK) –STE20/SPS1-related proline/alanine-rich kinase(SPAK) –NaCl cotransporter(NCC) phosphorylation cascade increases sodium reabsorption in distal kidney nephrons, resulting in salt-sensitive hypertension. The discovery of the WNK phosphorylation cascade has implications not only for rare inherited diseases but also for salt-sensitive hypertension associated with several (patho-) physiological conditions such as low-potassium diet and metabolic syndrome.

Hypertension is a common comorbidity associated with chronic kidney disease (CKD) and is also an important modifiable risk factor of CKD progression and cardiovascular disease. However, appropriate blood pressure control is often difficult to achieve due to increased salt-sensitivity in CKD. Recently, several studies suggest that not only reduced glomerular filtration but also increased renal tubular sodium reabsorption contributes to hypertension in CKD. However, involvement of WNK phosphorylation cascade in salt-sensitive hypertension in CKD is unknown. Moreover, the effect of immune systems on WNK kinases has not been investigated despite the fact that immune systems are important for salt sensitivity. To answer these questions, we investigated WNK phosphorylation cascade in three mouse CKD models (aristolochic acid nephropathy, adenine nephropathy, subtotal nephrectomy).

First, we created aristolochic acid nephropathy model. Protein abundance of WNK1, but not of WNK4, was increased at the distal convoluted tubules (DCT) in aristolochic acid nephropathy model. Accordingly, the phosphorylation of SPAK and phosphorylation of NCC was also increased. Moreover, a high-salt diet did not adequately suppress the activation of WNK1–SPAK–NCC phosphorylation cascade in aristolochic acid nephropathy model, leading to salt-sensitive hypertension. WNK1 protein abundance also was increased in adenine nephropathy, but not in subtotal nephrectomy, models.