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Regulation of WNK4-OSR1/SPAK-NCC Cascade by Dietary Sodium Intake

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Summary

Pseudohypoaldosteronism type II (PHAII) is an autosomal-dominant disorder characterized by hyperkalemia, acidosis, and hypertension. We recently found the activation of WNK-OSR1/SPAK-NaCl cotransporter (NCC) kinase cascade in the *Wnk4*^{D561A} knockin mice, a mouse model of PHAII. Phosphorylated NCC was concentrated on the apical plasma membranes of the distal tubules in the kidneys, resulting in increased thiazide-sensitive volume expansion and hypertension. To investigate whether this phosphorylation cascade is involved in physiological situations in addition to the disease state (PHAII), we measured the phosphorylation status of OSR1/SPAK and NCC in mice that were fed low-, normal-, and high-sodium diets. We found that the phosphorylation of OSR1/SPAK and NCC was increased by a low-sodium diet and decreased by a high-sodium diet and that this regulation by dietary sodium intake was completely lost in the *Wnk4*^{D561A} knockin mice. The increased phosphorylation under low-sodium diet was inhibited by spironolactone infusion, and the decreased phosphorylation under high-sodium diet was reversed by exogenous aldosterone infusion. Thus, the WNK4 -OSR1/SPAK-NCC cascade is a novel effecter system of aldosterone in the kidneys that regulates the body's sodium balance.