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WNK Kinase Links Salt-Sensitive Hypertension with Hyperinsulimenia

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Summary

The metabolic syndrome causes hyperinsulinemia and salt-sensitive hypertension. However, the mechanism responsible for this greater salt-sensitivity is still unknown. We recently demonstrated that constitutive activation of the WNK kinase-OSR1/SPAK kinase-NaCl cotransporter (NCC) phosphorylation cascade is the molecular pathogenesis of hypertension in pseudohypoaldosteronism type II (PHAII). In this study, we focused on one of the PHAII-causing mutants, WNK4 R1185C, and found that the mutation abnormally increased phosphorylation of WNK4 at 1190S, thereby activating the phosphorylation cascade. Since the 1190S constitutes an Akt/SGK consensus phosphorylation site, we further investigated whether 1190S phosphorylation of WNK4 was regulated by insulin. In MDCK and mpkDCT cells, insulin increased phosphorylation of WNK4 at 1190S, SPAK and NCC in a dose-dependent manner. Ly294002, a PI3K inhibitor, decreased the insulin effect on SPAK and NCC phosphorylation, indicating that insulin phosphorylates SPAK and NCC through PI3K in mpkDCT cells. Similar activation of the cascade was also observed in acute insulin-administered mice. However, such activation by insulin was not observed in WNK4 hypomorphic and SPAK deficient mice, confirming the existence of the insulin-WNK4-OSR1/SPAK-NCC signal cascade in the kidney. Moreover, hyperinsulinemic db/db mice fed a high salt diet indeed showed greater thiazide-sensitivity and increased WNK4, OSR1/SPAK, and NCC phosphorylation, compared with wild-type mice. To clarify the contribution of WNK and OSR1/SPAK to NCC phosphorylation, we mated db/db mice with SPAK(T243A/+) and OSR1(T185A/+) knock-in mice, whose SPAK and OSR1 cannot be phosphorylated by WNK kinases respectively. We found that NCC phosphorylation was decreased in SPAK(T243A/+) or OSR1(T185A/+) knock-in db/db mice. Compared to control mice, db/db mice showed increased blood pressure, which was disappeared in inactivated OSR1 or SPAK knock-in db/db mice. Thus, a novel regulatory mechanism linking hyperinsulinemia with salt-sensitive hypertension was identified. WNK4 may be a target molecule for the treatment of salt-sensitive hypertension under hyperinsulinemic conditions, such as obesity or metabolic syndrome.