RECENT PROGRESS IN UNDERSTANDING OF HYPERTENSION

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Uncontrolled hypertension is associated with increased risk of cardiovascular morbidity and mortality in general population. Renal salt handling is essential for volume regulation and blood pressure control. The kidney-specific Na-(K)-Cl cotransporters, NKCC2 and NCC, mediate salt reabsorption along the distal nephron thus determining the urinary salt excretion. Both transporters are regulated at the posttranslational level by phosphorylation / dephosphorylation reactions involving with no lysine [K] kinases (WNK) and the phosphatase calcineurin. Gain of function mutations of WNK1 or WNK4 kinases lead to increased phosphorylation and activity of NCC, salt retention, and hypertension, thus causing a genetic hypertensive syndrome known as pseudohypoaldosteronism type II (PHAII). Along the same line, pharmacological inhibition of calcineurin for immunosuppression in organ transplanted patients may cause hypertension due to impaired dephosphorylation of renal salt transporters resulting in their sustained activity. Our work contributed to understanding of the underlying pathophysiological mechanisms. We have characterized several mouse models of PHAII and clarified the role of calcineurin in the phosphoregulation of renal salt transporters. Moreover, our recent work and ongoing studies suggest that increased WNK-dependent phosphorylation and activation of NCC substantially contributes to hypertension in patients consuming a diet with high salt and low potassium content (Western diet). Pharmacological targeting of the WNK-pathway is therefore considered as a promising strategy for management of resistant hypertension forms.