

Abstract Submission No. : IL-9006

Chloride-sensing of WNK4: a novel mechanism of hypertension in potassium deficiency

Chih-Jen Cheng

Tri-Service General Hospital, National Defense Medical Center, Taiwan

Dietary potassium deprivation activates NCC whereas potassium loading turns off NCC. These effects on NCC are believed to be important for maintaining potassium homeostasis and in the pathogenesis of potassium deficiency-induced hypertension. Mechanistically, recent *in vitro* and *ex vivo* studies lend support for the hypothesis that extracellular potassium modulates intracellular chloride concentration to regulate the activity of NCC via WNKs-SPAK/OSR1 cascade. People have long proposed that there is an intracellular chloride sensor to initiate these responses.

Recent structural and *in vitro* results support that WNK kinases, particularly WNK4, may function as a chloride sensor. Here, we demonstrate that knockin mice carrying chloride-insensitive WNK4 mutant (L319F/L321F) phenocopy Mendelian disease and mouse model caused by gain-of-function mutations of WNK4. Furthermore, chloride-insensitive WNK4 knockin mice lose the expected WNK4-mediated stimulation of sodium-chloride cotransporter caused by hypokalemia-induced decreases in the intracellular concentration of chloride ion. Thus, WNK4 is a *bona fide* physiological intracellular chloride sensor. The results shed light on the pathophysiology of hypertension in potassium deficiency.