[SA-PO2763] γ-Adducin Functions as a Novel Regulator of the Thiazide-Sensitive NaCl-Cotransporter

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10:00 AM - 2:30 PM

Hypertension is projected to affect more than 1 billion individuals worldwide. The National Vital Statistics Report lists heart disease as the primary cause of death, affecting more than 20 million people in the United States alone. Primary hypertension remains a major risk factor for the development of cardiovascular and chronic kidney diseases. The thiazide-sensitive NaCl cotransporter (NCC) plays a key role in renal salt reabsorption and thereby the maintenance of systemic blood pressure. This study was designed to further elucidate the molecular mechanisms governing the regulation of NCC. Pull down experiments coupled to mass spectrometry identified γ-adducin as a novel interactor of the transporter. γ-Adducin co-localized with NCC to the distal convoluted tubule. $^{22}Na^{+}$ uptake experiments in the Xenopus laevis oocyte showed that γ-adducin stimulated NCC activity in a dose-dependent manner. The stimulatory effect of γ-adducin occurs upstream from the With-No-Lysine Kinase 4. The binding site of γ-adducin mapped to the N-terminus of NCC encompassing three previously reported phosphorylation sites. Furthermore, competition with the N-terminal domain of NCC abolished the stimulatory effect of γ-adducin on the transporter. γ-Adducin was unable to increase NCC activity when these phosphorylation sites were made constitutively inactive or active. In addition, γ-adducin bound only to the dephosphorylated N-terminal of NCC. Taken together, our observations suggest that γ-adducin functions as a dynamic regulator of NCC, likely by amending the phosphorylation state of the transporter and consequently its activity. These observations suggest a novel mechanism by which γ-adducin influences renal NaCl transport and hence blood pressure maintenance.

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