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Role of cGMP-Dependent Protein Kinase on Salt Sensitive Hypertension and the Significance of Vasodysfunction in Resistance Vessels via Activation in Sympathetic Nervous System.

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Summary

Background PKG1α can be stimulated by oxidation at cysteine42 (C42), by which an intermolecular disulfide linking is formed to enhance vasorelaxation in resistance vessels. However, the definition of C42 redox sensor in salt sensitivity is unknown.

Objective/Method We compared blood pressure (BP) with telemetry between wild-type (WT) PKG1α and the C42S mutant mice, and examined sodium balance in metabolic cages.

Results Non-reducing SDS-PAGE showed disulfide dimer of PKG1α only in WT kidney subjected to high salt diet. Interestingly, C42 oxidation required a greater increase in BP for sodium excretion than C42S without no differences in fluid retention between two genotypes. Importantly, Low/High Frequency ratio in BP variability, an indicator for sympathetic nervous (SN) activity, showed a significant elevation by salt loading in WT especially during dark period, while it was prevented in C42S. Activation of SN system in WT compared to C42S was recapitulated in either urinary norepinephrine (NE) excretion or renal NE content. We confirmed in immunohistochemistry that PKG substantially localized in nervous system such as dorsal root ganglia and also that neuron in renal cortex followed arterioles to and from glomerulus. We performed renal denervation (RDN) operation to assess if renal SN activity contributed to exacerbate salt sensitivity. RDN turned a decreased slope of pressure-natriuresis relationship in WT into about the same as C42S, whereas no further improvement in the slope from C42S. Increased NE spillover in WT was significantly suppressed by RDN, corroborating PKG1α oxidation ascribes salt sensitivity to NE biogenesis. To assess the mechanism of PKG1α oxidation in neuronal activity, we next transfected either $PKG1\alpha^{WT}$ or $PKG1\alpha^{C42S}$ into HEK-293T and compared NE-induced gene expression of c-fos, an early marker for neuronal activity. NE increased c-fos expression levels, but there were no differences between genotypes, suggesting PKG1α oxidation may not attribute to an efferent renal SN once SN system was equally activated.

Conclusion We demonstrated both SN activity and salt sensitivity can be ameliorated by preventing PKG1α oxidation. We propose C42 redox modification can be a novel therapeutic target for salt sensitive hypertension through regulation of SN system.