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The Role of PKG in Salt Sensitivity and the Excitatory Synapse through Activation in Sympathetic Nervous System

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Summary

PKG1α can be stimulated by oxidation at cysteine42 (C42), which leads to elicit vasorelaxation in resistance arteries. However, the significance of C42 oxidation in salt sensitivity remains unknown. We compared blood pressure changes to salt loading and fluid balance in mice harboring either wild-type (WT) PKG1α or the C42S mutant that is redox insensitive PKG1α. We found in non-reducing SDS-PAGE that disulfide dimer of PKG1α via C42 can be observed in kidney subjected to salt loading. Despite equivalent fluid retention between genotypes, BP increase for sodium excretion was required in WT greater than C42S. Intriguingly, low/high frequency ratio in BP variability, a sympathetic indicator, was elevated in WT during dark period, whereas was suppressed in C42S. Sympathetic activation in WT compared to C42S was recapitulated in urinary norepinephrine (NE) and renal NE content. Renal denervation (RDN) suppressed those NE levels and improved a decreased slope of pressure-natriuresis relationship in WT, while the slope didn't change much in C42S. The suppression of NE spillover by RDN corroborates PKG1α oxidation-related renal sympathetic activation gets involved in NE biogenesis. To assess the underlying mechanism, we checked neurotransmission between pre/post-synaptic neurons, using HEK293T or PC12 sympathetic neuron-like cells both transfected with either $PKG1\alpha_{WT}$ or $PKG1\alpha_{C42S}$. NE induced comparable c-fos upregulation between genotypes in both cells, suggesting neither NE reactivity in post-synaptic neuron nor the negative feed-back to pre-synaptic neuron appeared the mechanism of PKG oxidation-mediated sympathetic activation. Importantly, the upstream neurotransmitter acetylcholine increased NE release especially in PC12 cells expressing $PKG1\alpha_{WT}$. C42 oxidation activated tyrosine hydroxylase, a rate-limiting enzyme in NE biogenesis, by phosphorylating at ser40 in PC12 cells and mouse kidney as well. We reveal that PKG1α oxidation exacerbates salt sensitivity through sympathetic tone and propose that C42 redox sensor of is a useful therapeutic target for salt sensitive hypertension.