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The Novel Redox Regulation of cGMP-Dependent Protein Kinase (PKG1α) in Salt Sensitive Hypertension

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Summary

Background : Substantial studies have accumulated the evidence that intracellular cyclic GMP and the main effector of cGMP-dependent protein kinase 1α (PKG1α) exert protective effects against pathological stresses. PKG1α is activated primarily by cGMP binding, but it can be also stimulated with oxidant by forming disulfide bond between C42, where is located just proximal to cGMP binding sites and downstream from a protein interaction domain of leucine zipper. This oxidation is prevalent to relax resistant vessels, while it's detrimental in the heart, failing to prevent maladaptive hypertrophic responses. However, its significance on renal function especially in salt sensitive hypertension remains unknown.

Objectives : We tested the hypothesis that PKG oxidation, which impairs its capacity to counter renal injury, increases the salt sensitivity and thus induces hypertension.

Methods and Results : We compared BP response to salt loading, using cysteine redox insensitive PKG1α mice ($PKG1\alpha^{C42S}$) and the littermate controls ($PKG1\alpha^{WT}$). Western blotting and immunohistochemistry analyses showed PKG is diffusely expressed in renal cortex and medulla and that PKG forms intermolecular disulfide bond in kidney expressing $PKG1\alpha^{WT}$ only, which indicates PKG can be oxidized at C42 in kidney as well. As previously reported, we observed greater systolic BP in mice expressing $PKG1\alpha^{C42S}$ at baseline than $PKG1\alpha^{WT}$. However, salt loading didn't alter BP in $PKG1\alpha^{C42S}$, whereas it increased BP much in $PKG1\alpha^{WT}$. Importantly, this was accompanied by similar increases after salt loading in water intake, urinary volume, and urinary Na excretion regardless of the PKG1α genotypes. We also confirmed there was no difference in level of plasma aldosterone concentration between the two genotypes.

Conclusions : We revealed first evidence that PKG1α disulfide bond is observed in kidney and also that the redox regulation appears to be involved in salt sensitive hypertension.