No. 1827

The Reversible Salt Sensitivity Mediated through a Disparity of cGMP Signaling and the Therapeutic Application

Taishi Nakamura

Department of Medical Informatics Science and Administration Planning, Kumamoto University Hospital

Summary

Background Both nitric oxide and natriuretic peptide mediate natriuresis and vascular relaxation through cyclic GMP (cGMP) synthesis. PKG1α, a main effector of cGMP, is activated principally by cGMP binding, but it can be regulated with oxidant by forming an intermolecular disulfide bond across adjacent cysteine 42 residues (C42), where located at proximal end of each cGMP binding site. The redox mechanism is prevalent to relax resistant vessels and thus lessen blood pressure. However, the significance on salt sensitivity remains unclear.

Objective/Method We tested if C42 redox sensor in PKG1α controls salt sensitivity and renal pressure natriuresis, both which have long-term effects on sodium/water balance. Mice harboring either cysteine redox insensitive PKG1α ($PKG1\alpha^{C42S}$) or the littermate controls ($PKG1\alpha^{WT}$) were used to compare BP response to salt loading by means of telemetry system.

Results Non-reducing SDS-PAGE showed PKG forms disulfide dimer in kidney expressing $PKG1\alpha^{WT}$ only, indicating C42 locates in a key position to form an intermolecular disulfide bond. We confirmed in telemetry system that mice expressing $PKG1\alpha^{C42S}$ shows a modest hypertension when mice were fed with normal salt or low salt diet. However, salt loading didn't change BP at all in $PKG1\alpha^{C42S}$, while significantly increased the levels in $PKG1\alpha^{WT}$ predominantly during dark period. Importantly, we confirmed no differences in increased levels after salt loading such as water intake, urinary volume, and urinary sodium excretion regardless of PKG1α genotypes. Low frequency/high frequency ratio evaluated with heart rate variability in telemetry system, a marker of sympathetic nervous system (SNS), showed BP elevation in $PKG1\alpha^{WT}$ was accompanied with an activation in SNS.

Conclusions PKG1α disulfide dimer can be observed in kidney. The redox regulation in PKG1α appears to be involved in salt sensitive hypertension through renal sympathetic nervous system.