

The Mechanism of Salt-Sensitive Hypertension and Its' Induced Cardiac Diastolic Dysfunction

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Summary

Objectives: High salt-sensitivity is closely associated with the increase in cardiovascular events. However, the mechanism of high-salt-induced cardiovascular injury is unknown. The present study was undertaken to examine whether uncoupled of endothelial nitric oxide synthesis (eNOS) is involved in salt-sensitive hypertension and salt-induced cardiovascular injury (chronic kidney disease: CKD and cardiac diastolic heart failure: DHF).

Methods: (Experiment I) High-salt (HS) diet DS rats were orally given sapropterin (BH4) or hydralazine and were examined focusing on CKD. (Experiment II) Wild type (WT) and eNOS^{-/-} mice were compared on blood pressure rhythm and cardio-renal injuries. (Experiment III) We evaluated cardiac function by echocardiography, noninvasively assesses peripheral endothelial function as the reactive hyperemia-peripheral arterial tonometry index (RHI), and followed cardiovascular events. Moreover, we examined blood BH4/BH2 ratio, as the marker of eNOS uncoupling, in DHF patients.

Results: (Experiment I) DS rats exhibited severe albuminuria and renal eNOS uncoupling, assessed by eNOS dimer disruption and decrease of BH4/BH2 in renal tissue. BH4 significantly ameliorated albuminuria and prevented the development of renal remodeling (glomerular sclerosis and macrophage infiltration) in DS rats. This beneficial effect was associated with the attenuation of reactive oxygen species (ROS) by restoring eNOS uncoupling.

(Experiment II) Blood pressure of eNOS^{-/-} mice was significantly higher than that of WT, and eNOS^{-/-} mice exhibited a nondipper-type hypertension. Moreover, eNOS^{-/-} mice had the prominent glomerulosclerosis, the increased glomerular macrophage infiltration, and higher superoxide levels in glomerular tissues compared with WT.

(Experiment III) RHI in DHF patients were significantly lower than that in control patients, being accompanied by the significant decrease of blood BH4/BH2 ratio in DHF patients. Kaplan-Meier analysis demonstrated a significantly higher probability of cardiovascular events in the low RHI than in the high RHI. Multivariate Cox hazard analysis identified RHI and BNP as independent predictors of cardiovascular events.

Conclusions: These studied suggested that high salt sensitivity-induced CKD and nondipper-type hypertension are closely associated with eNOS dysfunction, so called "eNOS uncoupling". Furthermore, eNOS uncoupling-induced endothelial dysfunction independently correlated with future cardiovascular events, adding incremental clinical significance for risk stratification in patients with DHF.