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The Mechanism of Salt-Sensitive Hypertension and High-Salt-Induced Cardiovascular Injury - The Crucial Role of Reactive Oxygen Species and Apoptosis Signal-Regulating Kinase-1 -

EiichiroYamamoto [1], Osamu Yasuda [2], Shokei Kim-Mitsuyama [3], Keiichiro Kataoka [3]

[1] Department of Cardiovascular Medicine, Kumamoto University Hospital,
[2] Department of Cardiovascular Clinical and Translational Research, Kumamoto University Hospital,
[3] Department of Pharmacology and Molecular Therapeutics, Kumamoto University Graduate School of Medical Sciences

Summary

Obiectives: High-salt diet (HSD) is closely associated with the increase in cardiovascular events. However, the mechanism of high-salt-induced cardiovascular injury is unknown. The present study was under taken to examine whether apoptosis signal-regulating kinase (ASK) l is involved in salt-senstive hypertension and salt-induced cardiovascular injury.

Methods: (Experiment I) DS rats were orally given irbesartan (ARB), tempol (SOD mimetic), or hydralazine. (Experiment II) Wild type (WT) and ASK1-/- mice were fed a HSD for l0 weeks and the effects of HSD on cardiovascular injury were compared.

Results: (Experiment I) Irbesartan significantly ameliorated cardiac is chemia and prevented the development of cardiac remodeling in DS rats. This beneficial effect of irbesartan was associated with the attenuation of reactive oxygen species (ROS), the normalization of myocardial capillary density, and the inhibition of capillary endothelial apoptosis. Moreover, DS rats with cardiac hypertrophy and remodeling displayed the decreased myocardial VEGF expression and the increased cardiac ASKl activation, and irbesartan significantly reversed them. Tempol mimicked all the above mentioned effects of irbesartan, indicating the critical role of ROS. We also investigated the role of VEGF and ASKl in ROS-induced endothelial apoptosis, using cultured endothelial cells from WT and ASKl-/- mice. ROS-induced ASKl activation caused endothelial apoptosis and VEGF prevented endothelial apoptosis by inhibiting ASKl activation.

(Experiment II) HSD in WT and ASKl-/- mice similarly increased food intake, water intake, urine volume, and urinary sodium excretion, and comparably decreased plasma rennin activity (PRA) and aldosterone. Thus, ASKl appears to play a minor role in the increase in natriuresis and the decrease in PRA and aldosterone caused by HSD. HSD enhanced the cardiovascular phospho-ASKl in WT mice. HSD in WT mice enhanced cardiac TGF-β1, interstitial fibrosis, coronary perivascular fibrosis, and inflammatory cell infiltration, and these changes were associated with the increase in cardiac ROS and Nox2. ASKl deficiency abolished the above mentioned parameters. HSD also caused the impalrment of vascular endothelial dysfunction and increased vascular ROS and Nox2 in WT mice, while it did not cause vascular injury in ASK1-/- mice.

Conclusions: We obtained the first evidence that ROS-induced cardiac VEGF down regulation and ASKl activation, through enhancement of endothelial apoptosis, contributed to the decrease in myocardial capillary density, which was responsible for Ang II-induced cardiac injury. Furthermore, ASKl is implicated in cardiac inflammation and fibrosis and endothelial dysfunction caused by HSD, through the enhancement of ROS.