No. 1034

Novel Brain Molecular Mechanism Involved in Activation of the Sympathetic Nervous System through Acquisition of Salt-Sensitivity in Heart Failure with Pressure Overload and Therapeutic Approach

Yoshitaka Hirooka [1], Takuya Kishi [2], Koji Ito [3], Masaaki Nishihara [4], Masatsugu Nakano [4]

[1] Department of Cardiovascular Medicine Kyushu University Hospital, [2] Department of Advanced Therapeutics for Cardiovascular Diseases Kyushu University Graduate School of Medical Science, [3] Emergency & Critical Care Center Kyushu University Hospital, [4] Department of Cardiovascular Medicine Kyushu University Graduate School of Medical Sciences

Summary

Background and Aim: In a pressure overload model, sympathetic activity is augmented in response to high salt intake. Mineralocorticoid receptors (MR) and epithelial Na channels (ENaCs) are thought to contribute to Na-processing, but the underlying mechanism is unknown. Therefore, we investigated the contribution of the brain MR-ENaC pathway to salt-induced sympathetic activation in a pressure overload model.

Methods and Results: Aortic banding was performed to produce a mouse pressure overload model. Four weeks after aortic banding (AB-4), left ventricular (LV) wall thickness was increased without a change in percentage fractional shortening (%FS). Sympathetic activity increased in response to a 5-day high-salt diet in AB-4, but not in Sham-4. Brain MR, αENaC, and angiotensin II type 1 receptor (AT1R) expression levels were greater in AB-4 than in Sham-4. The increase in sympathetic activity and in the expression of these proteins was blocked by intracerebroventricular (ICV) infusion of eplerenone, a MR blocker. In another protocol, AB-4 mice were fed a high-salt diet (AB-H) for 4 additional weeks, %FS was decreased and sympathetic activity was increased in AB-H compared with Sham. Expression of MR and AT1R in the brain was higher in AB-H attenuated salt-induced sympathoexcitation and the decreased %FS, ICV infusion of eplerenone in AB-H attenuated salt-induced sympathoexcitation and the decreased %FS. ICV infusion of eplerenone also decreased brain AT1R expression. Oral administration of eplerenone had smaller effects on sympathetic activity and %FS than ICV infusion, although oral administration had greater effects on LV hypertrophy than ICV infusion.

Conclusions: These findings indicate that activation of brain ENaC and AT1R through MR contributes to the acquisition of Na sensitivity to induce sympathoexcitation. Therefore, high salt intake accelerates sympathetic activation and LV systolic dysfunction in a pressure overload model.