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# Pathophysiological Roles of Adrenomedullin Receptor Activity-Modifying Protein, RAMP2 in Salt-Sensitive Hypertension and Heart Failure

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Summary

Vasoactive peptides play central roles in the cardiovascular homeostasis, however imbalance between them may be the cause of various diseases. Adrenomedullin (AM) is a peptide originally identified as a vasodilating substance and it is now recognized as a pleiotropic peptide. Abnormality of AM production may be closely related with various diseases, such as hypertension, heart failure, and renal failure. In this study, we focused on AM and its receptor activity-modifying protein, RAMP2. Using knock out mice of AM and RAMP2, we investigated the pathophysiological roles of AM-RAMP2 system in hypertension and heart failure.

Both AM-/- and RAMP2-/- embryo died in utero at midgestation. In contrast, AM+/- and RAMP2+/- were apparently normal and we could obtain adult animals. Under the salt and angiotensin II (Ang II)-loading, AM+/- showed enhanced cardiac hypertrophy, cardiac fibrosis, and reduced cardiac function compared with wild-type mice. AM+/- also showed enhanced upregulation of hypertrophy and fibrosis-related genes in the heart. Protein synthesis of cardiac myocytes and proliferation of cardiac fibroblasts were both enhanced in AM+/-. In contrast, RAMP2+/- did not show significant changes compared with wild-type mice. Therefore, we next generated cardiac myocyte-specific RAMP2-/- mice by crossbreeding RAMP2-flox mice with αMHC-Cre recombinase transgenic mice, in which RAMP2 can be deleted by tamoxifen-treatment. Cardiac myocyte-specific RAMP2-/- mice showed cardiac dilatation, enhanced cardiac fibrosis, and reduced cardiac function.

These results show that endogenous AM-RAMP2 system work as organ-protective manner in hypertension and heart failure. AM-RAMP2 system could be a novel therapeutic target.