Genetic Models Revealed That Brain Natriuretic Peptide Regulates Cardiovascular Homeostasis Via Guanylyl Cyclase-A

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Summary

Natriuretic peptide family consists at least three endogenous ligands, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). These peptides can influence body fluid homeostasis and blood pressure control by their potent natriuretic, diuretic, vasorelaxant, and vascular growth inhibitory activities.

Brain natriuretic peptide (BNP), a cardiac hormone produced primarily by the ventricle, is thought to be involved in a variety of homeostatic processes via its cognate receptor, guanylyl cyclase-A (GC-A). We previously created transgenic mice with elevated plasma BNP concentrations (BNP-transgenic mice) and demonstrated that they exhibit reduced blood pressure and cardiac weight accompanied by a significant elevation of plasma cGMP concentrastions. To address whether BNP regulates cardiovascular homeostasis solely via GC-A, we have produced BNP-transgenic mice lacking GC-A (BNP-Tg/GC-A$^{-/-}$ mice) and examined their cardiovascular phenotypes. Plasma BNP concentrations in BNP-Tg and BNP-Tg/GC-A$^{-/-}$ mice (2734$\pm$480 and 1941$\pm$295 fmol/ml, respectively) were markedly elevated relative to GC-A$^{+/+}$ and GC-A$^{-/-}$ mice (<20 and 39.2$\pm$7.0 fmol/mal, respectively). No significant difference in plasma BNP concentration was noted between BNP-Tg and BNP-Tg/GC-A$^{-/-}$ mice. The GC-A$^{-/-}$ mice were hypertensive with cardiac hypertrophy relative to wildtype littermates, which is not alleviated by overexpression of BNP in BNP-Tg/GC-A$^{-/-}$ mice. This study therefore provides genetic evidence that BNP reduces blood pressure and cardiac weight through GC-A. The BNP-Tg/GC-A$^{-/-}$ mice provide the first experimental model demonstrating that BNP plays a role in cardiovascular homeostasis via GC-A.