Generation of Mice that Overexpress or Lack Natriuretic Peptide Family and Its Significance in the Regulation of Salt Metabolism

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Summary

Natriuretic peptide family consists at least three structurally-related 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. To examine the physiologic and pathophysiologic significance of natriuretic peptide family in cardiovascular regulation, we have tried to generate mice that overexpress or lack natriuretic peptide family.

To investigate the roles of BNP in the regulation of salt metabolism, we generated mice deficient in BNP and examined their cardiovascular phenotypes. A targeting vector was constructed in which the first and second exons of the 129/Sv mouse BNP gene were replaced by the neomycine resistance gene and was introduced into ES cells by the electroporation method. Homologus recombinants identified by genomic Southern blot analysis were injected into B6 mouse blastocysts, and mail chimeras generated were bred to B6 or 129/Sv females. Gene expressions of ANP and BNP were evaluated by Northen blot analysis. Plasma and cardiac concentrations of ANP and BNP were measured by radioimmunoassays specific for ANP and mouse BNP, respectively. Systolic blood pressure was measured by the tail-cuff method.

We obtained BNP-deficient (-/-) mice derived from three different recombinant ES cell clones. In hearts from -/- mice, neither BNP mRNA nor BNP-like immunoreactivity were detected. As compared with +/+ mice, ANP gene expression in the ventricle were augmented by 10-fold in -/- mice, which was observed as early as two days after birth. Plasma and ventricular ANP concentrations were also increased by 5- and 30- fold in -/- mice, respectivly, as compared with +/+ mice. No significant differences in systolic blood pressure were observed among +/+, +/-, and -/- mice on either standard (0.7% NaCl)- or high (8.0% NaCl)- salt diet.

We succeeded in the generation of BNP-deficient mice. The present study will provide insight into the physiologic and pathophypiologic roles of BNP in the regulation of salt metabolism.