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 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, we tried to generate mice that overexpress or lack natriuretic peptide family.

Using a targeting vector for the disruption of BNP, we produced several chimeric mice that transmitted the disrupted allele to their offsprings. We have obtained several wild-type, heterozygous, and homozygous mice and are currently examining their phenotypes including blood pressure and renal function. We also recently generated heterozygous and homozygous mice with the disruption of the 1st exon of the mouse CNP gene. We have obtained some chimeric mice and are checking whether they trasmitted the disrupted allele to their offsprings. Furthermore, we have recently constructed a second targeting vector for the disruption of the 1st and 2nd exons of the CNP gene and obtained several chimeric mice.

A 4.0-kb mouse CNP genomic fragment was isolated from a 129/Sv mouse genomic DNA library using the mouse CNP cDNA probe prepared by the 3'-RACE technique. The mouse CNP gene is composed of 3 exons separated by 2 introns. The 5'-flanking region contains an array of cis-acting regulatory elements and a dinucleotide CA repeat (microsatellite). Using the full-length mouse CNP genomic fragment isolated, it was possible to construct a targeting vector for the disruption of CNP, in which the 1st and 2nd exons of the mouse CNP gene would be disrupted.

We have previously developed transgenic mice with overexpression of BNP in the liver and showed that BNP is involved in the chronic blood pressure control. Three independent transgenic mouse lines with marked overexpression of BNP exhibited skeletal abnormalities of variable severity in proportion to plasma BNP concentrations. Skeletal abnormalities included kyphosis, crooked tails, and overgrowth of vertebrae and long bones. No gross abnormalities were found in the craniofacial portion of transgenic mice. Soft X-ray analysis revealed that BNP-transgenic mice have larger vertebral bodies in length, and elongated tibias and metatarsal bones compared to non-transgenic controls. Light microscopic examinations revealed overgrowth of the growth plate cartilage in vertebrae and long bones, both of which are formed by endochondral replacement. The BNP-transgenic mice exhibited overgrowth of the growth plate cartilage and hyaline-like cartilage formation in the intervertebral disc and ligament. The present study provides the first in vivo evidence that natriuretic peptides are involved in the process of endochondral ossification.