Natriuretic Peptide Family—— Physiological Significance and clinical implication

Kazuwa Nakao:2nd Division, Department of Medicine
Kyoto University School of Medicine
Hiroo Imura: Kyoto University

Summary

Following the discovery that the heart secretes atrial natriuretic peptide (ANP)with potent diuretic, natriuretic and vasorelaxing activities, brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) have been isolated from the porcine brain. ANP and BNP are elucidated to be the cardiac hormone mainly secreted from the atrium, and from the ventricle, respectively. CNP first recognized as the neuropeptide is now identified within the vascular wall, especially in endothelial cells and considered to be an autocrine/paracrine regulator. We have demonstrated that the natriuretic peptide family, as cardiac hormone, neuropeptide and local regulator, plays the pivotal role in blood pressure and body fluid homeostasis. In this study we tried to elucidate the physiological and clinical significance of natriuretic peptide family in salt handling mechanism using molecular biology technique, and seek for the clinical application of the natriuretic peptide family in salt homeostasis.

Since the primary structure of BNP is quite divergent among species and there exists striking species difference in structure-activity relationship, we first isolated mouse BNP gene and cDNA for generation of BNP over-expressing transgenic mice. Mouse BNP gene contains three exons and two introns. Typical TATAAA sequence exists about 100 base pairs upstream of the translation initiation site. In its 3'-flanking region, ATTTA repeat, which is considered to be involved in mRNA instability, was found. Mouse BNPmRNA is demonstrated to preferentially express in the atrium and the ventricle. By microinjecting the expression vector which contained cloned mouse BNP gene linked to human serum amyloid P promoter into mouse male pronucleus of fertilized egg, we succeed in obtaining several Fo transgenic mice with various copy numbers of BNP gene (up to 100 copies). By analysing these BNP over-expressing mice, the physiological significance of BNP in sodium balance is now under investigation.

We also succeed in cloning human BNP and CNP genes. In 1.8 kb of human BNP gene 5'-flanking region, there exists an array of putative cis-regulatory elements; AP-1 binding site, CT rich region, cAMP responsive element-like sequence. Isolated human CNP gene is composed of at least two exons and one intron. Its 5'-flanking region contains an inverted CCAAT box, two GC boxes and a cAMP responsive element-like sequence. The molecular mechanism of natriuretic peptide gene regulation in salt handling is further elucidated, using these cloned natriuretic peptide genes.