

Review

The role of the natriuretic peptides in the cardiovascular system

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Abstract

The discovery of the natriuretic peptide family was a breakthrough in modern cardiovascular physiology as it provided a direct link between the heart and the kidneys in the regulation of natriuresis. Along with vasopressin and the renin–angiotensin–aldosterone system, the natriuretic peptides comprise the key peptides on which our present understanding of neuroendocrine regulation of the cardiovascular system is based. Three natriuretic peptides have been identified; the A-type, B-type and C-type natriuretic peptides. The former two, the A- and B-type natriuretic peptides, function mainly in the cardiovascular system and comprise the cardiac natriuretic peptides. Together with our increased understanding of the neurohormonal regulation of the cardiovascular system in recent years, the discovery of the natriuretic peptide family was important in the establishment of the new field of cardiovascular endocrinology. © 2001 Elsevier Science B.V. All rights reserved.

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1. Overview and history

The history of the research on the natriuretic peptides can be traced back to 1956 when early studies using the electron microscope showed that granules similar to those in endocrine glands were found in the cells of the atria [1]. At the time, vasopressin and the renin–angiotensin–aldosterone system were known as regulators of natriuresis, but it was thought that there was another factor (called the ‘third factor’) which participates in natriuresis. It was also known from a clinical standpoint that natriuresis occurs following supraventricular attacks which suggested that this ‘third factor’ was linked to the heart [2].

A major discovery and advancement in the identification of atrial natriuretic peptide was made by de Bold in 1981 who showed that intravenous injection of atrial myocardial extract causes a rapid and potent natriuretic response in rats [3]. The hypothesis for this study was based on the fact that the numbers of atrial granules fluctuated with intravascular volume, and thus these atrial granules were

thought to be a regulator of intravascular volume [4]. Further advancement was made by Currie [5] who showed that the fraction showing natriuretic activity co-migrated with intestinal relaxation activity. This was an important finding as it allowed for fractionation and identification of atrial natriuretic peptide using gut smooth muscle relaxation as an assay for activity. The further purification and characterization of the factor by various groups throughout the world led to the discovery of atrial natriuretic factor, the first of the natriuretic factors, in 1983 and 1984 [6,7]. Important in the identification of the peptide by Kangawa and Matsuo was the use of heat to inactivate degrading enzymes which enabled them to sequence and identify an intact peptide which had not been degraded by proteases.

Subsequent studies were aimed at discovering family members which resulted in the isolation of two other factors which were named brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) [8,9]. It is important to note that these factors were known to exist as peptides based on studies by Matsuo who showed two activities (later determined to be BNP and CNP) which co-fractionated with ANP that showed intestinal relaxation activity.

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Studies also showed that although BNP was first isolated from the brain, that it is predominantly expressed in the ventricle. ANP and BNP were therefore renamed A-type and B-type natriuretic peptide, respectively, to better reflect their position in the family and to also lessen the misleading nature of the nomenclature of BNP as a cardiovascular and not a neural factor. ANP and BNP are the natriuretic peptides which are expressed predominantly in the atria and ventricle, respectively, and are referred to as the cardiac natriuretic peptides. CNP is differentially expressed mainly in the nervous system and vasculature (e.g. endothelial cells, monocyte/macrophages) and is involved mainly in neural regulation as well as vascular control although its role is still unclear.

2. Biochemical structure and properties

Each natriuretic peptide is coded by a separate gene but shows similar exon–intron properties suggestive of a common evolutionary ancestor. In humans, the ANP and BNP genes are located 8 kilobases apart on chromosome 1 and the CNP gene is located on chromosome 2 which is suggestive of evolutionary conservation between the cardiac natriuretic peptides ANP and BNP which is distinct from the predominantly neural peptide CNP [10–19]. At the cDNA level, BNP shows the least similarity among species but is unique in that a repetitive ATTTA-motif is found in the 3'-UTR. Although the precise role and mechanism of action of the ATTTA-motif is unknown, it is thought to regulate the half-life of mRNA and is commonly found in genes such as the interferons and lymphokines whose expression is increased in response to physiological stimuli then are rapidly degraded after loss of stimuli [20].

The gene product (i.e. protein) is highly conserved among species with ANP and CNP showing greater similarity across species as compared to BNP. Each natriuretic peptide gene produces a prohormone or precursor protein. ANP is synthesized as a 126 amino acid precursor protein which is cleaved to produce a 96 amino acid amino-terminal fragment and a 28 amino acid carbox-

yl-terminal fragment. The carboxyl-terminal 28 amino acid fragment is the biologically active peptide and has a shorter half-life than the amino-terminal fragment. Similarly, BNP is produced as a 108 amino acid precursor protein which is cleaved into a biologically active 32 amino acid carboxyl-terminal fragment and a 76 amino acid amino-terminal fragment. CNP produces 22 and 53 amino acid fragments with the former contained within the latter. The 22 amino acid fragment is the mature and more active form, and is expressed in the nervous system and endothelial cells. The common property of the natriuretic peptides is the formation of a disulfide bond which results in a ringed-structure (Fig. 1). The amino acids in the ringed-structure are highly conserved, and this structure is necessary for binding to its receptors. In contrast, the amino acids either amino-terminal or carboxyl-terminal to the ringed structure are quite divergent. As for the carboxyl-terminal tail, ANP and BNP have respectively five and six amino acid residues whereas CNP completely lacks this tail. The carboxyl-terminal amino acids of BNP affect its activity and its amino acid sequence is quite diverse among species.

3. Receptors and mode of action

The actions of the natriuretic peptides are modulated through their cognate receptors. Three receptors have been cloned to date which are known as the ANP-A (a.k.a. NPR-A, GC-A), ANP-B (a.k.a. NPR-B, GC-B) and ANP-C (a.k.a. NPR-C) receptors [21–27] (see Fig. 2). The ANP-A and ANP-B receptors form tetramers on the cellular membrane and have intracellular kinase and guanylate cyclase catalytic domains, and are thus involved in the cGMP-dependent signaling cascade. The ANP-C receptor lacks an intracellular domain. ANP and BNP both bind the ANP-A receptor with ANP to a higher preference than BNP. A BNP selective receptor has not yet been found. CNP shows high affinity for the ANP-B receptor. The ligand-binding domains of ANP-A and ANP-B show significant homology, and ligand binding to the receptor regulates activity of the intracellular catalytic domain

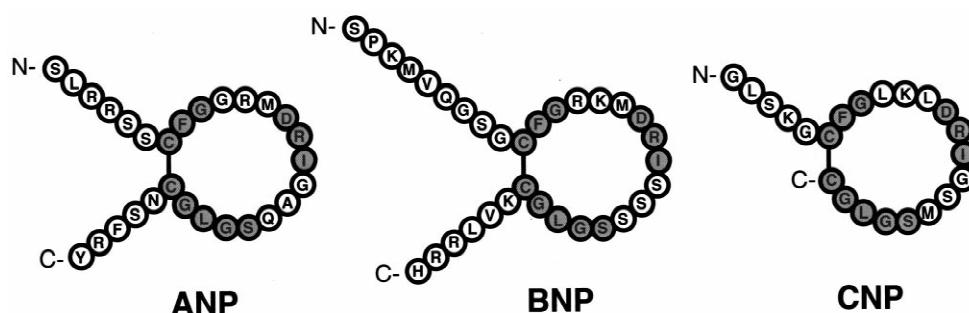


Fig. 1. Primary structure of A-, B- and C-type natriuretic peptides. ANP, BNP and CNP are 28, 32 and 22 residues, respectively. Conserved residues are shaded. Line denotes disulfide bond which results in a ringed-structure. Note the difference in the amino- and carboxyl-terminal ends.

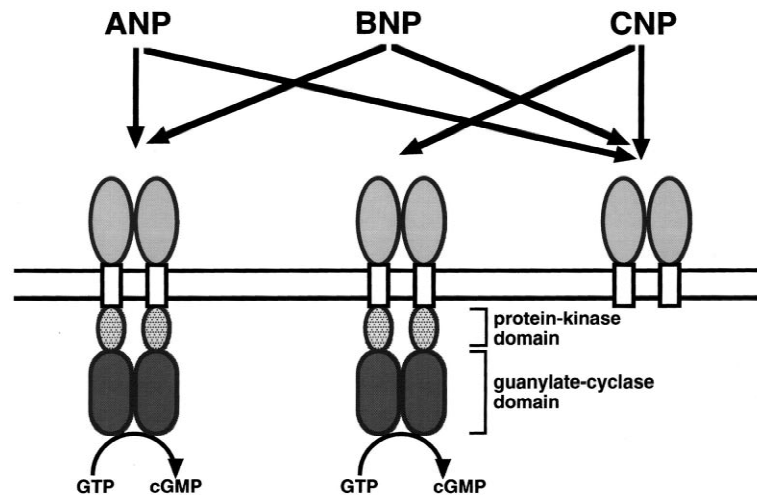


Fig. 2. Schematic illustration of the natriuretic peptide receptors. The ANP-A and ANP-B receptors have intracellular kinase and guanylate catalytic domains, and are involved in the cGMP-dependent signaling cascade. In contrast, the ANP-C receptor lacks an intracellular domain. ANP-A and ANP-B form tetramers on the cellular membrane. ANP shows a higher affinity than BNP for the ANP-A receptor.

through allosteric effects. The ANP-C receptor is thought to be involved in the clearance of the natriuretic peptides, but recent studies have also shown that it regulates cellular functions via coupling to g-proteins as well as the adenyl cyclase/cAMP system [28–32]. The ANP-A and ANP-B receptors differ in their expression; the ANP-A receptor is abundant in large blood vessels in contrast to the ANP-B receptor which is predominant in the brain. Both are commonly found in the adrenal glands and kidneys. In addition to clearance by the ANP-C receptor, they are also cleaved by neutral endopeptidase. Neutral endopeptidase is expressed in various tissues and recognizes all of the natriuretic peptides although it has a greater affinity for CNP than for ANP or BNP. ANP shows higher affinity than BNP for both the ANP-C receptor and neutral endopeptidase. The ANP-C receptor and neutral endopeptidase are thought to contribute in a combinatorial manner to the clearance of the natriuretic peptides.

4. Pharmacological effects

As hormones, the natriuretic peptides exert both peripheral as well as central (e.g. neural) effects [33,34]. ANP and BNP show common properties; CNP, however, is not natriuretic and is distinct in its properties. Peripheral effects include (1) natriuresis, (2) vasodilation, (3) inhibition of the renin-angiotensin and aldosterone system, and (4) anti-mitogenic effects on endothelial, smooth muscle and myocardial cells. Central effects include (1) thirst (water drinking) inhibition, (2) inhibition of salt appetite, (3) antipressor effects, and (4) inhibition of the hormones ADH and ACTH. Hormones such as endothelin, vasopressin and the catecholamines stimulate the secretion of ANP, and with the renin-angiotensin-aldosterone system

comprise a part of the neurohormonal control network of the cardiovascular system. ANP and BNP are major antagonizing agents of the renin-angiotensin-aldosterone system. In heart failure, ANP reduces pulmonary artery wedge pressure and systemic vascular resistance (i.e. reduction of preload and after load) while increasing stroke volume as well as a natriuretic and diuretic responses, and inhibits production of renin, aldosterone and norepinephrine. ANP contributes to vasorelaxation and natriuresis without additional activation of vasoconstricting neurohormones as well as sympathetic nerve control but vasodilation is attenuated in advanced heart failure [35,36]. BNP shows similar pharmacological effects but does not reduce norepinephrine levels. Atrial wall tension and increased intravascular volume are hemodynamic stimuli which increase the release of ANP. CNP is distinct as its secretion is little affected by hemodynamic stimuli. The actions of CNP in the cardiovascular system are likely to have a paracrine regulatory role on vascular tonus.

5. Animal genetic models

Early studies using spontaneous hypertensive rats (SHR) and stroke prone rats (SHR-SP) rats both showed increased gene expression and secretion of ANP from the ventricles suggesting that ANP is secreted from the ventricles in hypertensive hypertrophic hearts [37]. Studies using cardiomyopathic hamsters have shown that ANP synthesis in the ventricle is increased proportionate to the severity of heart failure [38,39]. These studies collectively showed in animal models that ANP is released from the ventricles in response to hemodynamic stress.

Transgenic as well as knockout mice are now available for ANP and BNP. ANP as well as BNP transgenic mice

showed chronic hypotension and reduced cardiac mass [40–42]. ANP knockout mice showed salt-sensitive hypertension suggestive of a role of this factor in salt-sensitive hypertension [43]. BNP knockout mice did not show salt-sensitive hypertension but instead showed cardiac fibrosis in response to ventricular pressure overload which suggests BNP is a cardiovascular anti-fibrotic factor possibly involved in cardiac remodeling [44]. In contrast, ANP-A knockout mice showed salt-resistant hypertension which suggests that the ANP-A signaling pathway can operate independently of ANP to dominate at the level of peripheral resistance [45].

6. Clinical implications

One of the important facets of the pathophysiological profile of the natriuretic peptides is the magnitude of fluctuation in circulating levels in pathogenic states. For BNP, circulating levels are at times increased by up to 1000 times of normal levels. Hormones act by binding to their receptors; down-regulation of these receptors in states of elevated hormonal levels act to negate the response of the hormonal stimuli. An important aspect of the cardiac natriuretic peptides is that infusion of ANP or BNP in patients with cardiac dysfunction induces a natriuretic response. This property of the cardiac natriuretic peptides has been exploited for their therapeutic effects. Recombinant ANP has been used for five years in Japan as treatment of congestive heart failure. Diuretic as well as vasodilatory effects are useful in acute heart failure cases, although adverse hypotensive effects are at times seen. Little, however, is known of the kinetics in the long term but use may be limited due to either or both receptor down-regulation and/or loss of effect due to decreased intravascular volume. Lack of an oral agent is also a limitation for long term use. BNP (e.g. Nesiritide) agents as well as endopeptidase inhibitors are also presently being developed.

Quantitative assessment of circulating levels of the cardiac natriuretic peptides has also been shown to be important to assess the degree of cardiac dysfunction [38,46–55]. Plasma ANP and BNP levels are both elevated in cardiac dysfunction in patients with heart failure. Plasma BNP levels better correlate with severity of left ventricular failure. Through past studies, the use of BNP levels as a diagnostic, therapeutic, and prognostic marker of left ventricular failure have been firmly established. BNP secretion and its circulating levels have been reported to correlate with individual components of the cardiac function (e.g. systolic contraction, diastolic dysfunction); however, given its properties as being a cardiovascular hormone secreted mainly from the heart in response to neurohormonal as well as hemodynamic stimuli, it is likely that the circulating cardiac natriuretic peptide levels reflect the cardiac state as a whole and will be useful in globally

understanding states in which there is cardiac stress. Ischemic myocardium is also associated with elevated cardiac natriuretic peptide levels. In acute myocardial infarction, BNP levels show two peaks, initially in the first 24 h and then again at the first week after onset. The first peak is thought to correlate with impairment in cardiac function, and the latter peak to reflect cardiac remodeling [56,57]. Importantly, the cardiac natriuretic peptides are the only available biochemical marker of the cardiac function. Biochemical diagnosis is non-invasive, fast, easy (e.g. non-technical) and cost-effective. Non-cardiologists will likely benefit most from use of this marker (e.g. hematologist using cardiac natriuretic peptide levels to diagnose the cardiac state in anthracycline cardiotoxicity [54]). Circulating cardiac natriuretic peptide levels used as a diagnostic marker with other screening methods such as chest X-ray and the electrocardiograph which are imaging and electrophysiological methods, respectively, should allow for a comprehensive and improved diagnosis of the cardiac state similar to the present combined use of biochemical, imaging and electrophysiological procedures in the diagnosis of acute myocardial infarction [55].

7. Conclusions

The natriuretic peptides since their discovery approximately 20 years ago have now been firmly established as being key factors in the regulation of intravascular volume and cardiovascular hemostasis, and have been critical in the establishment of the new field of cardiovascular endocrinology [58–60]. Not only do the cardiac natriuretic peptides play an important role in cardiovascular physiology but their applied use to the diagnosis and treatment of cardiovascular disease is presently an important topic of current research. Future studies while still necessary to understand the complex regulation of the cardiac natriuretic peptides will be important as a further step in advancing the medicine of cardiovascular endocrinology.

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