Natriuretic Peptides: Physiologic and Analytic Considerations

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KEYWORDS

• Natriuretic peptides • Heart • Physiology • Synthesis
• Receptors • Analysis

The concept of the heart as an organ with endocrine function is not new. After discovering that norepinephrine is synthesized in the heart in 1963,[1] Braunwald and colleagues[2] published a paper the following year in the *American Journal of Medicine* entitled: ''The heart as an endocrine organ.'' Although not scientifically documented before this seminal finding, the theory that the heart might possess endocrine functions emerged even earlier. In the 1950s, early electron microscopy investigations demonstrated the presence of electron dense ''specific atrial granules'' in the atria of the heart, which resemble secretory granules previously identified in endocrine cells.[3] Concomitantly, experiments showed that balloon stretching of the canine left atrium resulted in increased urinary flow.[4] However, the physiologic and pathophysiologic significance of the atrial granules remained obscure until de Bold, more than two decades later, demonstrated that atrial granularity was associated with changes in water and electrolyte balance,[5] and that homogenized atrial tissue injected into rats caused hypotension, diuresis and natriuresis.[6] In contrast, extract of ventricular tissue was ineffective in producing such effects. Based on these observations, de Bold proposed that the natriuretic response was elicited by an ''atrial natriuretic factor.'' In a remarkable series of subsequent scientific achievements, atrial or A-type natriuretic peptide (ANP) was rapidly purified, sequenced and synthesized.[7]

In 1988, researchers from Hisayuki Matsuo's group in Japan identified a peptide sharing structural features and biologic activity with ANP in porcine brain and named it brain natriuretic peptide (BNP).[8] Subsequent experiments soon made it clear that the heart is the main source of BNP in the circulation;[9] B-type natriuretic peptide is currently the most commonly used name of this peptide. Soon after the discovery of BNP, Matsuo's research group identified a third member of the natriuretic peptide family from porcine brain, C-type natriuretic peptide (CNP).[10]

In the late 1980s, it also became clear that the N-terminal fragment of the ANP prohormone, proANP, was circulating in human plasma,[11] and in the mid 1990s, the N-terminal fragment of the BNP prohormone was also detected in the human circulation.[12] This article provides an overview of the physiology of the natriuretic peptides, with an emphasis on BNP and NT-proBNP, and highlights some analytic considerations of significance to the clinician.

PHYSOLOLOGIC CONSIDERATIONS

Natriuretic Peptides

The natriuretic peptide family encompasses several genetically distinct peptide hormones that share structural features (**Fig. 1**), possess important physiologic properties, including natriuresis, diuresis, vasorelaxation, sympatho-inhibition,[13] growth inhibition,[14] and anti-fibrogenic mechanisms,[15] and are central players in cardiovascular, endocrine and renal homeostasis (**Fig. 2**).[16] ANP and BNP in the circulation are

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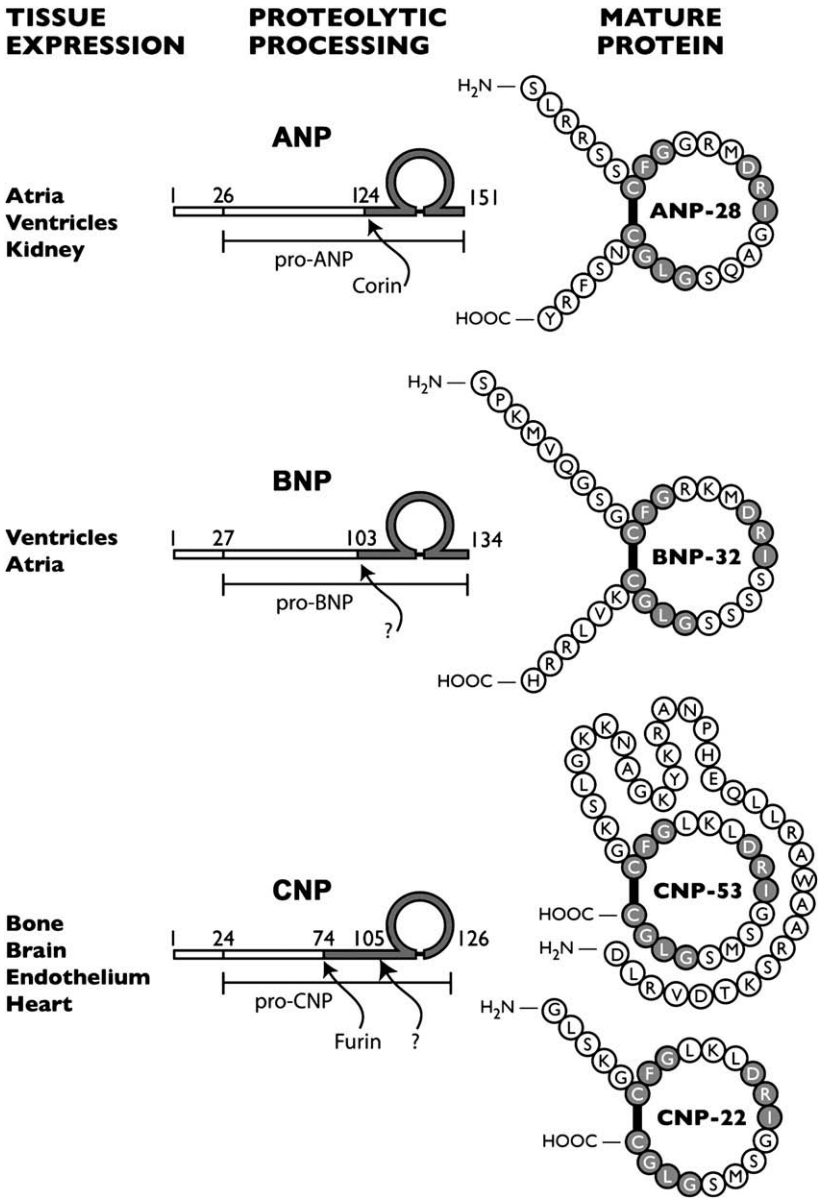

Fig. 1. Natriuretic peptide expression, processing, and structure: ANP, BNP and CNP are expressed as pre-pro-hormones. The signal sequences are removed to form pro-ANP, pro-BNP and pro-CNP. The peptides are further proteolytically processed to form mature peptide hormones. proANP is cleaved by corin. The enzymes responsible for proBNP cleavage are thought to be furin and corin, but this contention has not been definitively verified. proCNP is cleaved by furin in vitro into a 53 amino acid peptide, which is further processed to a 22 amino acid form by an unknown protease. All peptides contain a conserved 17 amino acid disulfide linked ring structure that is required for biologic activity. Invariant residues within the ring structure are shaded. (*From* Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. Endocr Rev 2006 February;27(1):47–2; with permission.)

derived primarily from the myocardium.[9] In contrast, CNP is primarily produced by vascular endothelium cells and in the central nervous system.[17] D-type natriuretic peptide, found in the venom of the green mamba (Dendroaspis angusticeps);[18] urodilatin, derived from alternative processing of proANP in the kidney;[19] and the intestinal epithelium-derived peptides guanylin and uroguanylin[20] also share primary structure features with ANP, BNP and CNP. Different natriuretic peptides may—to a variable degree—exert their actions in an autocrine, paracrine, or