The natriuretic peptides
An introduction

Abstract The natriuretic peptides are a family of widely distributed, but evolutionarily conserved, polypeptide mediators that exert a range of actions throughout the body. In cardiovascular homeostasis, the endocrine roles of the cardiac-derived atrial and B-type natriuretic peptide (ANP and BNP) in regulating central fluid volume and blood pressure have been recognised for two decades. However, there is a growing realisation that natriuretic peptide actions go far beyond their volume-regulating effects. These pleiotropic actions include local (autocrine/paracrine) regulatory actions of ANP and BNP within the heart, and of another natriuretic peptide, CNP, within the vessel wall. Effects on function and growth of the local tissue environment are likely to be of great importance, especially in disease states where tissue and circulating levels of ANP and BNP rise markedly. At present, the relevance of other natriuretic peptides (notably uroguanylin and DNP) to human physiology and pathology remain uncertain. Other articles in this issue of Basic Research in Cardiology review the molecular physiology of natriuretic peptide signalling, with a particular emphasis on the lessons from genetically targeted mice; the vascular activity of natriuretic peptides; the regulation and roles of natriuretic peptides in ischaemic myocardium; and the diagnostic, prognostic and therapeutic roles of natriuretic peptides in heart failure.

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Discovery of the natriuretic peptides

Almost from the earliest days of electron microscopy, electron-dense “specific atrial granules” were described in the cardiac atria, possessing many of the morphological features of secretory granules in endocrine cells [14, 17]. The physiological function of these granules and the nature of their secreted product remained mysterious until revealed by the painstaking and highly original work of Adolfo de Bold and colleagues working in Ontario through the 1970s. In 1979, De Bold described how atrial granularity was altered according to systemic water and electrolyte balance [6]. The following year, he and his colleagues provided a seminal description of how atrial tissue extracts promoted intense diuresis and natriuresis in rats [8]. This observation provided a remarkable demonstration of the endocrine activity of the cardiac atria and described the existence of an hormonal “atrial natriuretic factor”. It is noteworthy, and perhaps of no little encouragement to all, that the manuscript describing this work – now a citation classic – was rejected for publication by the Journal of Clinical Investigation in 1980, but was published the following year in Life Science. In 1982, de Bold confirmed the relationship between atrial granularity and the natriuretic factor [7]. The structure of the atrial polypeptide hormone that we now know as atrial natriuretic peptide (ANP) was confirmed by Flynn et al. in 1983 [10].

In 1988, Sudoh et al. isolated a peptide with similar biological activity to ANP from porcine brain [31]. The peptide was named “brain natriuretic peptide” (BNP) although the cardiac ventricles were subsequently found to be the major source of circulating BNP [22] (The nomenclature “ventricular natriuretic peptide”, VNP, is
occasionally encountered in the wider biological literature.) Two years after the discovery of BNP, Sudoh et al. [32] described a further, structurally similar peptide from porcine brain which they named CNP. Subsequently, endothelium has been identified as a major site of CNP synthesis. Other structurally related peptides include DNP from the venom of the green mamba, *Dendroaspis angusticeps*; urodilatin which is a product of alternative processing of pro-ANP by renal cells; guanylin and uroguanylin which are expressed by intestinal epithelium [18]. In this introduction I will focus on ANP, BNP and CNP.

### Synthesis and storage of natriuretic peptides

The products of ANP and BNP gene expression are high molecular mass prepropeptides. Proteolytic cleaving produces proANP and proBNP which are the stored forms in myocyte granules. CNP is synthesised as a propeptide. The major biological activity of all three peptides resides in low molecular mass “mature” peptide fragments, possessing a common 17 amino acid ring structure composed of a number of invariant amino acids.

#### ANP

The human ANP precursor peptide gene (*Nppa*) encodes a 151 amino acid preprohormone that is proteolytically processed to form a 126 amino acid prohormone (proANP1-126) that is stored in atrial myocyte granules [26]. ProANP is cleaved during the release process by a cardiac protease, corin, to form proANP1-98 (N-terminal ANP), and the biologically active 27 amino acid carboxy-terminal peptide (ANP99-126) [36]. Although expressed under physiological conditions primarily in the atrium, the induction of left ventricular preproANP gene expression is seen in many clinical disorders and experimental disease models [30]. Markedly less preproANP mRNA is present in the normal adult ventricle although this increases in pathological states, such as heart failure [29]. Plasma ANP concentration increases rapidly in response to pressure as well as volume loading [19, 30].

#### BNP

Human BNP is synthesised as a 132 amino acid pre-propeptide that is processed by endoprotease cleaving to a 108 amino acid precursor protein (proBNP1-108). The propeptide is cleaved into the biologically active 32 amino acid carboxy-terminal fragment and a 76 amino acid N-terminal fragment [31]. Unlike ANP, which is stored as the 126 amino acid propeptide, the most abundant form of BNP in atrial myocardium in humans is the mature 32 amino acid peptide [13, 15] (45 amino acids in rat [1, 24]). Mature BNP is secreted by both the cardiac atria and the ventricles although the ratio of ventricular-to-atrial preproBNP mRNA is higher than that observed for ANP. The cardiac ventricle is the main source of BNP secretion in contrast to ANP, where secretion in health occurs from the atrium [22].

#### CNP

From a 103 amino acid CNP pro-peptide, two CNP fragments are produced: CNP22 and CNP53, the former sequence being contained within the latter. The 22 amino acid fragment may be regarded as the mature and more biologically active form. The major sites of CNP expression are the nervous system and endothelial cells. Heart tissue contains little CNP and, only small amounts if any are found in plasma [5, 33, 38].

Continuous, basal release of ANP and BNP from myocardium ensures the presence of the peptides in plasma at low concentrations. The release of ANP and BNP from myocardium is stimulated by a wide variety of physical, physiological, pathological and chemical stimuli. The marked augmentation of circulating natriuretic peptides in clinical conditions characterised by left ventricular dysfunction has been the focus of huge interest. There is now overwhelming evidence that BNP release in particular is closely associated with the degree of left ventricular dysfunction and has diagnostic and prognostic significance. The important area of BNP in heart failure