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REVIEW

Natriuretic Peptides in ESRD

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• **Natriuretic peptides are involved in the regulation of volume homeostasis. Their levels generally are increased in the setting of volume expansion and act on multiple effector systems to cause vasodilation and natriuresis in an effort to return volume status back to normal. In patients with end-stage renal disease, the natriuretic capabilities of these peptides are limited. However, there has been much interest in the potential applicability of measurement of these peptides as a surrogate marker of volume status and in the determination of dry weight. Furthermore, atrial natriuretic peptide and brain natriuretic peptide can serve as markers of left ventricular dysfunction and may have utility in determing cardiac prognosis in patients on long-term dialysis therapy.** ***Am J Kidney Dis*** **46:1-10.**

INDEX WORDS: Natriuretic peptides; end-stage renal disease (ESRD); dialysis; volume regulation.

NATRIURETIC PEPTIDES are a well-described family of hormones with a major role in sodium and body volume homeostasis.[1] Atrial natriuretic peptide (ANP), brain natriuretic peptide (also known as B-type natriuretic peptide; BNP), C-type natriuretic peptide (CNP), D-type natriuretic peptide, and their prohormones, along with urodilatin (also known as renal natriuretic peptide), compose the major members of this family (Table 1). Adrenomedullin is a separate peptide that also has a role in volume homeostasis. A host of other peptides, such as guanylin, uroguanylin, melanocyte-stimulating hormone, and a putative endogenous ouabain-like factor also likely have a role in the regulation of body volume, but are not discussed in this review.[1] The synthesis and release of these peptides are stimulated by various derangements in systemic blood pressure, as well as increases in extracellular volume and sodium balance. They exert a multitude of endocrine and paracrine actions in the heart, brain, kidneys, vasculature and adrenal glands. However, their major role is to induce natriuresis through their actions on renal hemodynamics and tubular function. Other effects of natriuretic peptides include vasodilation, decrease in sympathetic outflow, inhbition of arginine vasopressin release, and inhibition of aldosterone release.[1] In patients without renal function (end-stage renal disease [ESRD]), their role in inducing natriuresis obviously is limited. However, these peptides may have other important hemodynamic effects in patients with ESRD by virtue of their pleiotrophic effects on the vasculature, sympathetic nervous system, and adrenal gland. Furthermore, there has been much interest in the possibility that natriuretic peptide levels may serve as markers of both volume overload and overall prognosis.

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Table 1. Natriuretic Peptides

	Site of Production	Stimulus	Primary Effect
ANP	Cardiac atria	Atrial wall tension and stretch	Reduction in plasma volume and blood pressure
BNP	Cardiac ventricle	Ventricular wall tension	Same as ANP
CNP	Heart, brain, kidney, vasculature	Shear stress	Vasodilation, ?central nervous system neurotransmitter
D-Type natriuretic peptide	Unknown	Unknown	Vasodilation
Guanylin Uroguanylin	Gastrointestinal mucosa	Unknown	Regulates salt and water transport
Adrenomedullin	Adrenal medulla, cardiac ventricles, lungs, kidneys	Unknown	Reduction in plasma volume, blood pressure, vasodilation

PHYSIOLOGY OF NATRIURETIC PEPTIDES IN PATIENTS WITH NORMAL RENAL FUNCTION

Natriuretic peptides, with the exception of adrenomedullin, share important structural elements that are required for receptor-mediated cell signaling. Chief among these features is a common 17–amino acid ring structure that shares a high degree of sequence homology between members of the family.[2] Structural divergence between peptides is largely restricted to differences in the N- and C-terminal portions and probably has an important role in differentiating the function of the particular peptide. For example, urodilatin (renal natriuretic peptide) differs from ANP only in the addition of 4 amino acids in the N-terminal region.[3] This translates into similar binding affinities of the peptide for their receptors, but urodilatin appears more potent in inducing natriuresis, likely through a postreceptor effect.[4] The complexity of the natriuretic peptide family is increased further by the finding that peptides derived from the prohormone of ANP (such as the N-terminal fragment $ANP_{1\text{-}98}$) also can have natriuretic ability.[5]

Natriuretic peptides respond to increases in extracellular fluid volume sensed by atrial (ANP) and ventricular (BNP) stretch receptors, as well as by increased shear stress on endothelial cells (CNP).[1,6] However, there are important differences in stimuli for secretion of various natriuretic peptides. The major stimulus for ANP secretion is atrial stretch or distention, which is reflected in clinical studies by the direct relationship between right atrial pressure and plasma ANP concentration.[7] In addition to stimulating secretion of previously synthesized ANP, which is stored in secretory granules, atrial stretch also quickly leads to an increase in ANP gene transcription and messenger RNA abundance.[8] This highly regulated pathway of secretion for ANP also is influenced by other factors, including endothelin (stimulates ANP secretion), glucocorticoids (stimulates ANP gene expression), vitamin D (inhibits ANP expression and secretion), and the autonomic nervous system.[9-12] BNP is unlike ANP in that it is not stored in secretory granules and its release is dependent on continued transcription and translation of its gene.[13]

Release of BNP from the endocardium is constitutive, but also modulated by both pressure and volume overload of the left ventricle.[14] This is reflected by the strong correlation between left ventricular (LV) chamber size and LV end-diastolic pressure with BNP levels.[15] The differ-

Table 2. Natriuretic Peptide Receptors

Receptor	Ligand Specificity	Second Messenger	Tissue Distribution
NPR-A	ANP > BNP ≫ CNP	cGMP	Kidney, adrenal, endocardium, brain, lung, aorta
NPR-B	CNP ≫ ANP > BNP	cGMP	Kidney, adrenal, cerebellum, pituitary, lung
NPR-C	CNP > ANP, BNP	None known	Widely distributed