A Is For . . .

Natriuretic Peptides

Natriuretic peptides *A family of vasoactive peptide hormones released mainly from cardiac myocytes, causing natriuresis and diuresis and having other physiologic effects.*

Landmark papers identifying and characterizing natriuretic peptides were published by Japanese investigators in the mid-1980s, though the presence of secretory granules in atrial myocytes and a natriuretic response to atrial myocyte stretch had been reported long before.

Atrial natriuretic peptide (ANP) was described first, followed by B-type or brain natriuretic peptide (BNP), which was isolated from pig brain but is synthesized primarily by cardiac ventricular myocytes. ANP and BNP have similar structures and actions. C-type natriuretic peptide (CNP), also found first in brain, is structurally and functionally different and is expressed mostly in the central nervous system and vascular tissue.

Myocyte stretch stimulates release of ANP and BNP. Both hormones are synthesized as precursor proteins and modified to prohormones. Pro-ANP is stored in granules; regulation of its secretion seems to occur at that level. On release into the circulation, the prohormone is cleaved into the active hormone (ANP) and an N-terminal fragment.

Regulation of BNP release is at the level of gene expression, which increases rapidly upon an appropriate stimulus. Pro-BNP is not stored but is released and at once cleaved into BNP and N-terminal BNP.

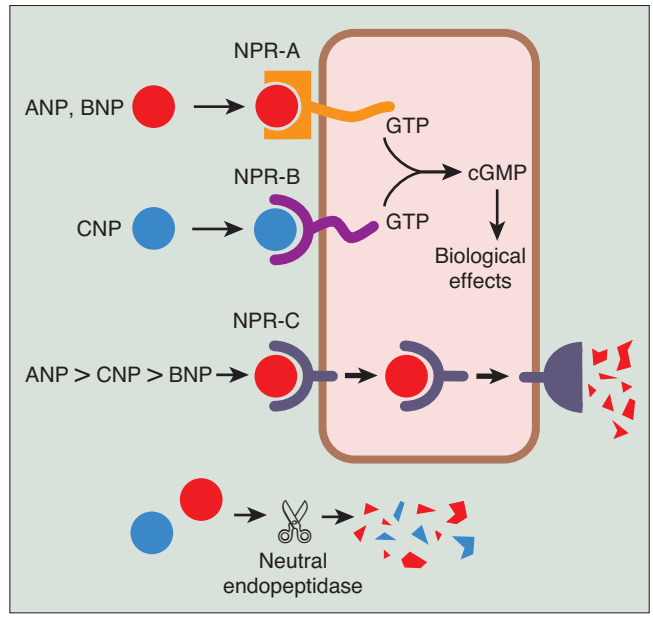
Targets for ANP and BNP are endothelial cells, smooth muscle cells, cardiac myocytes, renal epithelium, and fibroblasts. Three natriuretic peptide receptors have been described, among which NPR-A and B are guanylyl cyclase receptors involved in the physiologic effects while NPR-C is a clearance receptor.

In the kidney, ANP and BNP increase glomerular filtration and inhibit sodium reabsorption, causing natriuresis and diuresis. Natriuretic peptides relax vascular smooth muscle, reducing blood pressure and ventricular preload. ANP and BNP block cardiac sympathetic nervous system activity and inhibit the renin-angiotensin-aldosterone axis. BNP also has direct relaxing effects on the myocardium.

CNP acts locally in the vasculature as a vasodilator and inhibitor of cell proliferation. It also has several functions in the central nervous system.

Recent attention has focused on circulating levels of natriuretic peptides as markers of heart disease. In patients with suspected heart failure, BNP or N-terminal BNP predicts disease state and prognosis better than ANP or N-terminal ANP. Assays for N-terminal BNP are available.

Similarly, the physiologic properties of ANP and BNP make them ideal agents to treat heart failure. Recombinant human BNP (nesiritide) is in late-stage clinical development, though trials have assessed hemodynamic benefit and safety rather than reduction in clinical events. Whether this expensive agent has any advantages over dobutamine, nitroglycerine, or diuretics has not been determined.



Binding of natriuretic peptides to the A and B receptors on target cells generates cyclic GMP, a second messenger that mediates most of the biological effects. ANP and BNP bind preferentially to NPR-A, and CNP to NPR-B. Lower affinity of the clearance receptor NPR-C for BNP contributes to a longer plasma half-life for BNP than for ANP. The peptides are also inactivated by neutral endopeptidase, a zinc metallopeptidase present on target cells.

An alternative approach is to potentiate the effects of endogenous ANP and BNP by inhibiting neutral endopeptidase, an enzyme that is upregulated in heart failure. Neutral endopeptidase also degrades bradykinin and adrenomedullin, which are vasodilators, and endothelin-1 and angiotensin II, which are vasoconstrictors.

Unpredictable effects of neutral endopeptidase inhibition on vascular tone can be avoided by combining angiotensin-converting enzyme and neutral endopeptidase inhibition. Omapatrilat is the prototype in this new class of drugs, termed *vasopeptidase inhibitors*.

A suggestion from a phase II study that omapatrilat would be more effective than lisinopril in patients with heart failure was not borne out by a phase III trial. Another concern is angioedema, which in another study occurred three times as often in patients given omapatrilat than in those who took enalapril. Angioedema is thought to be caused by increased circulating levels of bradykinin, which is inactivated by both ACE and neutral endopeptidase.

RECENT REVIEWS

James A. de Lemos, et al: B-type natriuretic peptide in cardiovascular disease. *Lancet* 362:316-322, 26 July 2003.

M.A. Weber: Vasopeptidase inhibitors. *Lancet* 358:1525-1532, 3 Nov 2001.