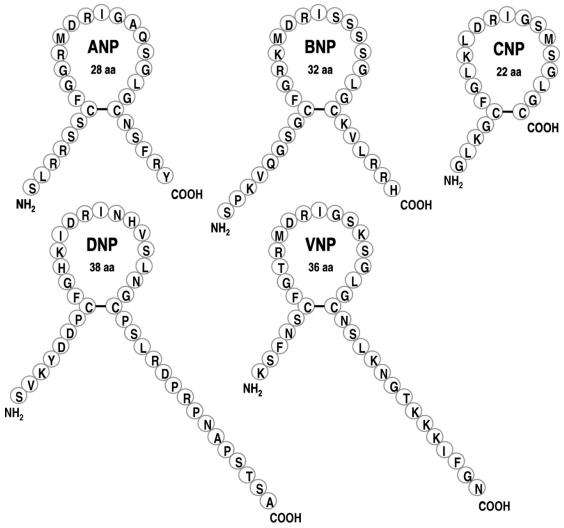
Evolution of natriuretic peptides-Current applications in human and animal medicine

The ABC of natriuretic peptides



- Atrial natriuretic peptide (ANP)
  - Produced in both atria
  - Triggered by increased atrial-wall tension following increased intravascular volume or pressure
  - Stored in granules to be released
  - Urodilatin-version of ANP found in the kidneys
    - Produced in renal distal tubules
    - Locally controls sodium and volume
    - Decreases renin secretion from macula densa
    - Inhibits aldosterone release from zona glomeruosa
    - Inhibits angiotensin II-stimulated proximal tubular Na^+ and H_2O reabsorption
- B-type natriuretic peptide (BNP)
  - Found predominantly in the ventricles
  - Rapidly produced by cardiomyocytes w/ myocardial stretch & hypoxia
  - Actions:
    - Diuresis and natriuresis via direct tubular actions (as above for urodilatin)
    - Inhibits cardiac sympathetic nervous system
    - Inhibits RAAS by suppressing norepinephrine and aldosterone levels
    - Anti-proliferative, antifibrotic and relaxation effects on heart and vascular tissues

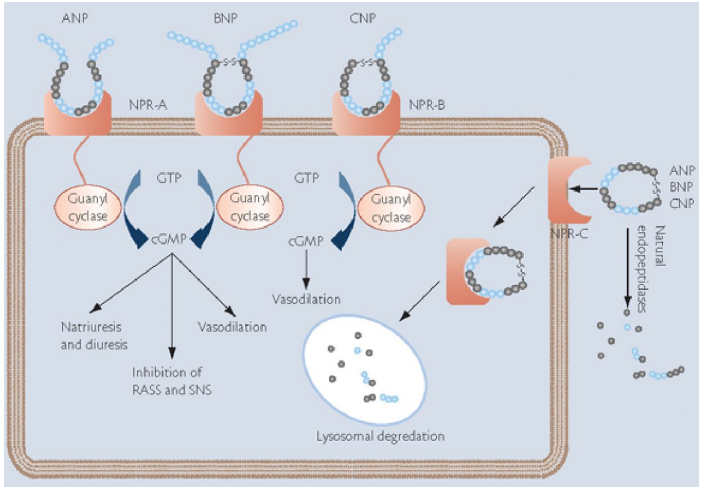
Actions of Natriuretic peptides

Renal	Vascular	Cardiac	SNS/RAAS
↑GFR	↓Arterial Tone	Lusitropic	↑Vagal tone
↓Na^+ resorbtion	↓Venous tone	Antifibrotic	↓SNS activity
	Antiproliferative	Antiproliferative	↓Renin release
			↓Aldosterone release

- C-type natriuretic peptide (CNP)
  - Paracrine and autocrine functions
  - Found in vascular endothelial cells, central nervous system, kidney, chondrocytes, pituitary gland
  - Actions:
    - Neurotransmitter function
    - Regulation of vascular tone
    - Inhibition of fibroblast activation
    - Role in enchochondral ossification
    - Role in testicular endocrine function, spermatogenesis and adequate placental function during pregnancy
    - Minimal diuretic/natriuretic actions
- Dendroaspis natriuretic peptide (DNP)
  - Isolated from the venom gland of the green mamba-unknown function
- Ventricular natriuretic peptide (VNP)
  - Role in the fluid homeostasis of primitive ray-finned bony fish

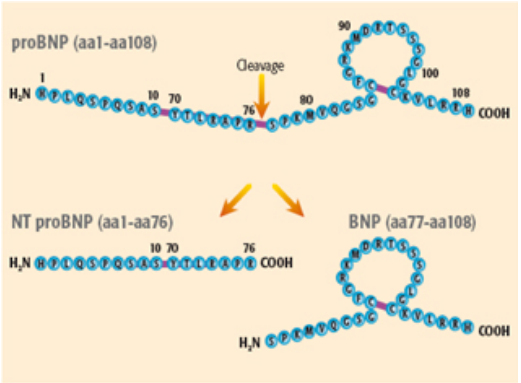
Natriuretic peptide receptors and neutral endopeptidase

- Natriuretic peptide receptor A
  - Expressed in lungs, brain, heart, adrenals, kidney, and terminal ileum
  - Actions:
    - Production of intracellular cGMP
    - Leads to further signal transduction
    - Natriuresis, inhibition of renin and aldosterone
    - Vasorelaxation
    - Anti-fibrotic, anti-hypertrophic and lusitropic
- Natriuretic peptide receptor B
  - Expressed in lungs, brain, skin, adrenals, kidneys, uterus and ovaries
    - Expression in veins predominantly over arteries
    - Activated predominantly by CNP
  - Actions:
    - Production of intracellular cGMP
    - Mediates vasorelaxation by actions on smooth muscle
    - Has a hypotensive effect in comparison to NPR-A



- Natriuretic peptide receptor C
  - Expressed in lungs, brain, heart, adrenals, kidneys, mesenterium, fat tissue, placenta, veins and aorta
  - Modulates naturetic peptide activity at target organs-ie downregulates NP activity
- Natriuretic peptide receptor D-only found in the eel
- Neutral endopeptidase
  - Induced by adenylate cyclase, glucocorticoid, thrombin, calcitonin, and cytokines
  - Actions
    - Inactivation of enkephalins, neuropeptides (ie substance P) and β-amyloid peptide
    - Active elimination of natriuretic peptides from circulation by hydrolysis

Processing of pre-proBNP and its products



- Pre-proBNP
  - Stimulated production by cardiomyocytal stretch and ischemia/hypoxia
  - Also stimulated by
    - Endothelin-1
    - Angiotensin-II
    - Interleukin 1 β
    - Adrenergic agonists
  - Rapid removal of an amino acid terminal results in proBNP
- proBNP cleaved into two parts by corin or furin
  - Forms NT-proBNP and the active substance BNP
- Elimination of BNP via NPR-C, neutral endopeptidase activity, and renal clearance
- NT-proBNP cleared entirely by the kidneys

BNP and NT-proBNP testing in humans and animals

- Human testing considerations
  - BNP levels are decreased in obesity and increased in kidney disease
  - Excellent in predicting prognosis in short and long term for acute or chronic heart failure
  - Also useful in the full spectrum of cardiovascular diseases
  - Decreases in NT-proBNP was associated with improved outcome
- Veterinary applications
  - BNP able to discriminate between heart failure and non-heart failure in dogs and is correlated with severity of heart failure
    - Confirmed on two separate studies (DeFrancesco 2007 and Oyama 2008)
  - In comparing BNP to NT-proBNP, the later was diagnostically superior in evaluating canine respiratory distress
  - Aortic banding in 6 male beagles showed NT-proBNP to be better correlated with LVEDP compared to NT-proANP

Questions

1. Interaction of BNP with NPR-A will ultimately result in
   a. Inositol triphosphate production
   b. Protein kinase activation
   c. Diacylglycerol production
   d. Adenylyl cyclase activation
2. List two mechanisms of elimination of BNP
   a. NPR-C
   b. Neutral endopeptidases
3. As opposed to ANP, BNP is
   a. Stored in granules for release
   b. Triggered by increased atrial wall tension
   c. Homologous to urodilatin
   d. Stimulated for production during stretch of cardiomyocytes
4. CNP predominantly exerts its effects
   a. In a paracrine and autocrine manner
   b. On angiotensin II-mediated sodium reabsorption mechanisms
   c. On aquaporin channels in ray-finned bony fish
   d. On osteoblasts
5. Diagram the processing of pre-proBNP to active BNP