



REVIEW ARTICLE

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Regulation of atrial natriuretic peptide (ANP) and its role in blood pressure

Feroz Ahmed, *Nahida Tabassum, Saima Rasool

Department of Pharmaceutical Sciences, Pharmacology Division, University of Kashmir, Srinagar-190 006, India

ABSTRACT

Atrial natriuretic peptide (ANP) a powerful vasodilator, and a protein (28-amino acid peptide) hormone secreted by heart muscle cells. It is released in response to atrial distention, stretching of the vessel walls, sympathetic stimulation of β -adrenoceptors, raised sodium concentration, angiotensin-II and endothelin. ANP binds to three cell surface receptors called ANP receptors. The overall effect of ANP on the body is to counter increases in blood pressure and volume caused by the renin-angiotensin system. It has also been reported to increase the release of free fatty acids from adipose tissue. Regulation of its effects is achieved through gradual degradation of the peptide by the enzyme neutral endopeptidase (NEP). Inhibitors of NEP are currently being developed to treat disorders ranging from hypertension to heart failure. Synthetic analogs of ANP have been investigated as potential therapies for the treatment of decompensated heart failure and other diseases.

Key Words: Atrial natriuretic peptide, ANP receptors, Hypertension, Angiotensin.

INTRODUCTION

Atrial natriuretic peptide (ANP), atrial natriuretic factor (ANF), atrial natriuretic hormone (ANH), or atriopeptin, is a powerful vasodilator, and a protein (polypeptide) hormone secreted by heart muscle cells. It is involved in the homeostatic control of body water, sodium, potassium and fat (adipose tissue) (Widmaier *et al.*, 2008). ANP is the most abundant of a family of at least three structurally and functionally related peptide hormones that exert widespread effects on cardiovascular and renal function. Under normal hemodynamic conditions, it is predominantly synthesized, stored, and secreted in a regulated fashion by modified myocytes of the cardiac atria. However, in pathophysiological conditions of hemodynamic overload (in congestive heart failure, ventricular synthesis of the peptide) it is reactivated and contributes significantly to the circulating pool of the peptide. In lesser amounts, it is synthesized in some peripheral tissues, in the vasculature, and in central nervous structures (Potter *et al.*, 2009).

ANP is a 28-amino acid peptide with a 17-amino acid ring in the middle of the molecule. The ring is formed by a disulfide bond between two cysteine residues at positions 7 and 23. ANP is closely related to BNP (brain natriuretic peptide) and CNP (C-type natriuretic peptide) and all have the same amino acid ring (De Bold, 1985).

REGULATION OF ANP

ANP is produced, stored and released by cardiac myocytes of the atria of the heart. It is released in response to atrial stretch and a variety of other signals induced by hypervolemia, exercise or caloric restriction (Widmaier *et al.*, 2008). The hormone is constitutively expressed in the ventricle in response to stress induced by increased afterload (e.g. increased ventricular pressure from aortic stenosis) or injury (e.g. myocardial infarction). The secretion of ANP is regulated by following factors:

Atrial distension

Plasma concentration of ANP increases in response to volume expansion in anesthetized rats (Lang *et al.*, 1985). Experiments in chloralose-anesthetized dogs have demonstrated that mitral valve obstruction, increases plasma ANP levels which is not

*Corresponding Author:

Dr. Nahida Tabassum

Associate professor, Pharmacology Division

Department of Pharmaceutical Sciences

University of Kashmir, Srinagar, J & K, India-190006

E-mail: n.tabassum.uk@gmail.com

Contact No.: +91-9419407326

Table 1: Types of ANP receptors (Widmaier *et al.*, 2008).

No.	Type	Name
1	GC-A NPRA/ANPA or NPR1	Guanylyl cyclase-A Natriuretic peptide receptor-A
2	GC-B NPRB/ANPB or NPR2	Guanylyl cyclase-B Natriuretic peptide receptor-B
3	NPRC/ANPC or NPR3	Natriuretic peptide clearance receptor-B

attenuated by vagotomy (Ledsome, 1985). ANP has been found to increase in humans with water immersion (Epstein *et al.*, 1989), in clinical conditions such as heart failure (Tikkanen *et al.*, 1985) and renal failure (Rascher *et al.*, 1985). Rate of contraction has been suggested to stimulate ANP secretion (Schiebinger and Linden, 1986). ANP secretion is substantially augmented in experimental animals with cardiac hypertrophy or heart failure where gene expression of the hormone is increased in both the atria and ventricles (Ruskoaho, 1992).

Cardiac ischemia

Ischemia is one of the most potent stimuli for ANP secretion, which can be viewed as an important homeostatic mechanism since ANP can produce cardiac vasodilatation to increase blood flow and oxygen delivery to the heart as well as peripheral vasodilatation to reduce arterial pressure. The reduction in cardiac after load results in a beneficial reduction in cardiac oxygen demand. Nocturia, seen with obstructive sleep apnea, has recently been attributed to increased secretion of ANP. Plasma ANP levels in sleep apnea correlate directly with the degree of hypoxemia but also could be stimulated by hemodynamic mechanisms such as pulmonary hypertension, which elevates right heart pressures. Also, myocardial infarction leads to acute cardiac ischemia and a profound increase in the release of ANP in both animals (Tikkanen *et al.*, 1987) and humans (Tan *et al.*, 1989).

Endothelin

Endothelin-1 is one of the most potent stimuli for ANP secretion (Lew and Baertschi, 1989). Endothelin increases ANP secretion and up-regulates ANP messenger RNA in isolated rat cardiac myocytes. It has been proved that a specific endothelin-1 receptor antagonist attenuates the ANP response to

atrial stretch (Skvorak *et al.*, 1995), thus demonstrating that endothelin plays an essential paracrine role in the stretch-activated ANP secretory process. High atrial pressure (8–10 mmHg) produces a marked increase in ANP secretion (30–60 min) compared to the low atrial pressure control period. Endothelin further augments this response when added while atrial pressure is elevated (60–90 min) (Pollack *et al.*, 1997).

Nitric oxide (NO)

NO is a potent vasodilator which is produced from L-arginine and increases the production of c GMP in both cardiac muscle and vascular smooth muscle (Moncada *et al.*, 1991). An infusion of the NO synthase inhibitor, NG-nitro-L-arginine methyl ester (L-NAME), when given to conscious rats augments ANP secretion in response to blood volume expansion (Leskinen *et al.*, 1985). ANP secretion is increased by 150% by increasing atrial pressure from 2 to 10 mmHg (Skvorak *et al.*, 1996).

Angiotensin II, Vasopressin and Adrenergic agonists

Angiotensin, vasopressin and phenylephrine when infused in anesthetized rats produce changes in the plasma concentration of ANP correlated directly with changes in atrial pressure (Katsube *et al.*, 1985). An increase in plasma ANP in rats occurs with angiotensin infusion at doses that did not alter atrial or left ventricular end-diastolic pressures (Lachance *et al.*, 1988). *In vitro* studies have produced contradictory results. Several vasoconstrictor hormones including norepinephrine, epinephrine, angiotensin II and vasopressin can increase ANP secretion by indirect mechanisms related to vasoconstriction and increased atrial and ventricular stretch.

Neurohumoral factors

Calcium: It plays a central role in secretion mechanisms of many hormones. ANP secretion is found to be independent of changes in extracellular calcium even in the presence of EGTA, a calcium chelator (De Bold, 1989). BAY K 8644, a calcium channel agonist that increases calcium entry into cardiac myocytes and increases cardiac contractility, is found to stimulate ANP secretion in atrial myocyte cultures (Irons *et al.*, 1992). It is also postulated that calcium has a negative effect on ANP secretion under basal conditions but a positive modulatory

role under conditions of stimulated sustained release (Doubell *et al.*, 1994).

Nucleotides: For ANP secretion both cAMP and cGMP appear to be inhibitory. Forskolin, which increases cellular cAMP, inhibits ANP secretion in atrial myocytes (Iida and Page, 1988; Muir *et al.*, 1993). A number of humeral factors appear to inhibit ANP secretion by stimulating cAMP including adrenomedullin, α -adrenergic agents such as isoproterenol, (Muir *et al.*, 1993) histamine, (Li *et al.*, 2003) and phosphodiesterase-3 inhibitors (Cui *et al.*, 2002). Also, cGMP inhibits ANP and appears to mediate the actions of nitric oxide and C-type natriuretic peptide on ANP secretion (Lee *et al.*, 2000).

Prostaglandins: It has been demonstrated that prostaglandins play a critical role in the stimulus secretion mechanism for ANP secretion. PGF₂ α and PGE₂ but not PGI₂ stimulate ANP synthesis and secretion in rats in vivo and in cultured rat atrial myocytes (Gardner and Schultz, 1990). Others have reported that prostaglandins are a potent stimulator of ANP secretion in rat ventricular myocytes and rabbit atria sections (Gardner *et al.*, 1992).

Kinases: Several protein kinases have been implicated in the stimulus-secretion coupling for ANP secretion. Phorbol esters, which increase the cellular concentration of protein kinase C (PKC), stimulate ANP secretion from the isolated rat heart (Ruskoaho *et al.*, 1986). Staurosporine, a protein kinase inhibitor, blocks Forskolin-induced inhibition of ANP secretion in the perfused rabbit atria (Cui *et al.*, 2002). It has been found that the tyrosine kinase inhibitor, lavendustin, blocks stretch-induced ANP release (Taskinen *et al.*, 1999). However, a study has also shown that another tyrosine kinase inhibitor, genistein, stimulates ANP release.

CONCLUSION

ANP plays a determining role in long-term regulation of arterial pressure. At normal salt intake, ANP by itself is not the determining factor in renal regulation of salt excretion but only one of several redundant natriuretic mechanisms, whose activity may not be absolutely essential in isolation. However, ANP-mediated antagonism of RAS is essential

for the cardiovascular and renal adaptations to chronically elevated dietary salt intake. The overall effect of ANP on the body is to counter increases in blood pressure and volume caused by the renin-angiotensin system.

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