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Atrial Natriuretic Peptide in Cardiovascular Biology and Disease (*NPPA*)

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Abstract

Atrial natriuretic peptide (ANP) is a cardiac hormone that regulates salt-water balance and blood pressure by promoting renal sodium and water excretion and stimulating vasodilation. ANP also has an anti-hypertrophic function in the heart, which is independent of its systemic blood pressure-lowering effect. In mice, ANP deficiency causes salt-sensitive hypertension and cardiac hypertrophy. Recent studies have shown that ANP plays an important role in regulating vascular remodeling and energy metabolism. Variants in the human *NPPA* gene, encoding the ANP precursor, are associated with hypertension, stroke, coronary artery disease, heart failure (HF) and obesity. ANP and related peptides are used as biomarkers for heart disease. Recombinant proteins and small molecules that enhance the ANP pathway have been developed to treat patients with HF. In this review, we discuss the role of ANP in cardiovascular biology and disease.

Keywords

ANP; Corin; Heart failure; Hypertension; Natriuretic peptides; Sodium homeostasis

1. Introduction

Maintaining salt-water balance is of fundamental importance for all animals. The discovery of the natriuretic activity in rat atrial extracts by de Bold *et al*. established a previously suspected cardiac endocrine function in regulating body fluid homeostasis (de Bold et al., 1981). The responsible molecule later was found to be atrial natriuretic factor (ANF), also called atrial natriuretic peptide (ANP) (de Bold, 1985). Under high blood volume and pressure, heart muscle cells release ANP into the circulation. In the kidney, ANP enhances

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salt and water excretion. In the blood vessel, ANP promotes vasodilation. As such, ANP acts as a cardiac hormone to regulate blood volume and pressure. Defects in the ANP pathway now are known to contribute to major diseases such as hypertension, cardiac hypertrophy and heart failure (HF). More recently, ANP and related peptides have been implicated in lipid metabolism and metabolic disease. In this review, we discuss the role of ANP in cardiovascular biology and disease.

2. The *NPPA* gene

In mammals, the natriuretic peptide family has three members: ANP, brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) (Potter et al., 2006; Wu et al., 2009). These peptides are encoded by three separate genes evolved from an ancestral natriuretic peptide gene in primitive vertebrates (Inoue et al., 2003; Takei et al., 2006). The human *NPPA* gene, encoding the ANP precursor, is on the short arm of chromosome 1 (1p36.21). The gene consists of 3 exons and spans more than 2 kb in length. The *NPPB* gene, encoding the BNP precursor, has a similar genomic structure and is located ~10 kb upstream of the *NPPA* gene. Most likely, these genes were derived from gene duplication. In contrast, the human *NPPC* gene, encoding the CNP precursor, is on the long arm of chromosome 2 (2q37.1), indicating that it was segregated from the *NPPA* and *NPPB* genes during evolution (Takei et al., 2006).

The *NPPA* gene is expressed primarily in the heart, where the expression level is higher in atria than ventricles (Potter et al., 2006). Low levels of ANP expression have been detected in other tissues, including the lung, aorta, brain, adrenal gland, kidney and uterus. Transcription factors including GATA-4, NF-AT-3 and TBX5 are critical for *NPPA* expression in the heart (Durocher and Nemer, 1998). These transcription factors also play a role in the expression of other cardiac genes (Molkentin et al., 1998; Pan et al., 2002). To date, the transcriptional regulation of *NPPA* expression in non-cardiac tissues is not well understood.

3. ANP biosynthesis and processing

ANP is synthesized as a precursor, *i.e.* prepro-ANP, a polypeptide of 151 amino acids (Fig. 1). In the endoplasmic reticulum, signal peptidase removes the 25-amino-acid signal peptide, which may be further processed by signal peptide peptidase and released from the cell. Small fragments derived from the ANP signal peptide have been detected in human plasma (Pemberton et al., 2012). After the removal of the signal peptide, the 126-amino-acid pro-ANP is stored in the granules in cardiomyocytes. When the cells are stimulated, for example, by mechanical stretch, pro-ANP is released and converted to mature ANP by corin, a serine protease anchored on the cell surface (Wu et al., 2002; Yan et al., 1999). The corin-mediated activation cleavage occurs at Arg-98↓Ser-99 in pro-ANP (Yan et al., 2000), generating a 98-amino-acid N-terminal peptide, *i.e.* NT-pro-ANP, and a 28-amino-acid C-terminal peptide, *i.e.* ANP. In mice, disrupting the *Corin* gene abolished pro-ANP processing and caused spontaneous hypertension (Chan et al., 2005; Wang et al., 2012b), indicating that corin is the primary pro-ANP convertase *in vivo*. In humans, *CORIN* variants and mutations that impair corin activity have been identified in patients with hypertension

and heart disease (Dong et al., 2013; Dries et al., 2005; Wang et al., 2012a; Wang et al., 2008; Zhang et al., 2014).

ANP is degraded by at least two different mechanisms. After binding to the natriuretic peptide receptor C (NPR-C), also called the clearance receptor, which is expressed in many tissues, ANP is internalized and degraded in lysosomes (Koller and Goeddel, 1992; Potter et al., 2006). Alternatively, ANP is degraded by neutral endopeptidase (NEP), also called neprilysin, a zinc-dependent protease that inactivates ANP at Cys-105↓Phe-106 and other sites (Kenny and Stephenson, 1988) (Fig. 1). Inhibition of neprilysin increases ANP levels. In HF patients, combined inhibition of neprilysin and angiotensin receptor represents a novel therapeutic strategy to reduce the mortality and morbidity (McMurray et al., 2014).

In non-cardiac tissues, pro-ANP may be processed at alternative sites. Urodilatin, for example, is a 32-amino-acid ANP isoform from human urine, which contains four additional amino acids (Thr-Ala-Pro-Arg) at the N-terminus (Feller et al., 1989) (Fig. 1). In animal models and healthy volunteers, urodilatin exhibited potent natriuretic and diuretic activities (Forssmann et al., 2001). Urodilatin appeared more resistant than ANP to NEP-mediated degradation (Gagelmann et al., 1988). To date, the proteolytic enzyme responsible for producing urodilatin in the kidney remains unclear. Because urodilatin is cleaved at Leu-94↓Thr-95, it is unlikely that the enzyme is a trypsin-like protease such as corin, which cleaves after basic residues (Knappe et al., 2003).

4. Biological functions of ANP

The primary function of ANP is to promote natriuresis and diuresis in the kidney and to relax vascular smooth muscles, thereby regulating blood volume and pressure. This function is mediated by the natriuretic peptide receptor A (NPR-A), also called guanylyl cyclase A, a transmembrane receptor containing an intracellular guanylyl cyclase domain (Koller and Goeddel, 1992; Potter et al., 2006). Upon ANP binding, the receptor is activated, promoting cyclic guanosine monophosphate (cGMP) production. Increased intracellular cGMP levels activate cGMP-dependent protein kinases (PKGs), which in turn increase glomerular filtration rate, inhibit sodium and water reabsorption in the proximal tubules and collecting ducts, and suppress renin secretion from the juxtaglomerular cells (Theilig and Wu, 2015; Zeidel, 1990). In smooth muscles, PKG activation lowers intracellular Ca^{2+} concentration and decreases the sensitivity of the contractile apparatus to Ca^{2+}, thereby relaxing the muscle cells (Carvajal et al., 2000). ANP also inhibits aldosterone production in the adrenal gland (Kudo and Baird, 1984; Maack et al., 1984). Consistently, knockout mice lacking *Nppa* or *Npr1* gene developed hypertension (John et al., 1995; Lopez et al., 1995) and had high levels of plasma and renal renin activities (Melo et al., 1998; Shi et al., 2001).

ANP and BNP are believed to share the same receptor. The binding affinity for BNP to NPR-A, however, is ~10-fold weaker than that for ANP (Koller and Goeddel, 1992), suggesting that ANP is the primary ligand for NPR-A. In mice, ANP- and BNP-deficiencies resulted in different phenotypes; ANP knockout mice were hypertensive, whereas BNP knockout mice were normotensive but developed cardiac fibrosis (John et al., 1995; Tamura et al., 2000). These results suggest that ANP and BNP may not substitute each other for the

same receptor *in vivo*. It has been reported that another BNP receptor may exist (Goy et al., 2001). To date, however, such a receptor remains unidentified.

In the heart, ANP has a local anti-hypertrophic function that is independent of its systemic blood pressure lowering effect. In *Nppa* and *Npr1* knockout mice, dietary or pharmacological treatments lowered blood pressure, but did not prevent cardiac hypertrophy (Feng et al., 2003; Knowles et al., 2001). Conversely, overexpression of NPR-A in the heart did not alter blood pressure, but reduced cardiac myocyte size in both wild-type and *Npr1* knockout mice (Kishimoto et al., 2001). Moreover, heart-specific *Npr1* knockout mice had normal blood pressure, but exhibited marked cardiac hypertrophy (Holtwick et al., 2003). It has been shown that ANP-stimulated cGMP production leads to cGMP-dependent protein kinase-I activation and phosphorylation of transient receptor potential canonical-6 Ca^{2+} channels and the regulator of signaling-2, an angiotensin II receptor type 1 downstream molecule, thereby antagonizing hypertrophic responses in cardiomyocytes (Kinoshita et al., 2010; Klaiber et al., 2011; Klaiber et al., 2010; Tokudome et al., 2005). A recent study indicated that ANP-mediated cGMP increase caused subcellular redistribution of phosphodiesterases 2 and 3, which modulated cardiac contractility by enhancing β_1-adrenergic receptor/cAMP signaling and decreasing β_2-adrenergic receptor/cAMP signaling (Perera et al., 2015). Such an alteration between β_1- and β_2- adrenergic receptor/cAMP signaling may serve as a compensatory mechanism in response to hypertrophic stress in the heart (Kuhn, 2015).

Vascular remodeling is an important physiological process (Korshunov et al., 2007; Mulvany et al., 1996). ANP has been shown to inhibit vascular smooth muscle cell proliferation (Hutchinson et al., 1997; Itoh et al., 1990) and regulate endothelial cell growth, migration and permeability (Itoh et al., 1992; Lara-Castillo et al., 2009; Sabrane et al., 2005), which are important in angiogenic processes (Kuhn et al., 2009; Tokudome et al., 2009). During pregnancy, spiral artery remodeling in the uterus is critical for increasing uteroplacental blood flow. Impaired spiral artery remodeling has been identified as an underlying mechanism in pregnancy-induced hypertension (Pijnenborg et al., 2006). Studies have indicated that corin-mediated ANP production in the uterus is important for spiral artery remodeling (Zhou and Wu, 2013). In *Corin* and *Nppa* knockout mice, uterine spiral artery remodeling was impaired, causing gestational hypertension and proteinuria (Armstrong et al., 2013; Cui et al., 2012). In humans, *CORIN* variants associated with preeclampsia were reported in a Caucasian population (Stepanian et al., 2014) and *CORIN* mutations reducing corin activity were identified in preeclamptic patients (Cui et al., 2012; Dong et al., 2014). Consistent with these findings, low levels of plasma corin were associated with the risk of preeclampsia (Khalil et al., 2015).

It has been shown that ANP is also involved in energy metabolism. In isolated adipocytes and healthy volunteers, ANP promoted lipolysis in a cGMP-dependent manner (Lafontan et al., 2008; Moro et al., 2004; Sengenes et al., 2000; Sengenes et al., 2003). In adipocytes, ANP enhanced mitochondrial respiration and the brown fat thermogenic program via a PKG-p38 mitogen-activated protein kinase (MAPK)-mediated pathway (Bordicchia et al., 2012). Moreover, ANP stimulated fat oxidation in skeletal muscles (Engeli et al., 2012; Miyashita et al., 2009). These ANP actions may be important in preventing metabolic

diseases. Consistently, low plasma ANP levels were associated with obesity and type 2 diabetes (Magnusson et al., 2012; Wang et al., 2007; Wang et al., 2004b). In patients with hypertension and HF, low plasma ANP levels were associated with the metabolic syndrome (Hsieh et al., 2013; Wang et al., 2013). More recently, glucagon-like peptide-1, a gut-derived hormone, was found to increase ANP secretion from the heart, thereby lowering blood pressure in mice (Buglioni and Burnett, 2013; Kim et al., 2013). Thus, ANP may serve as a part of the extended endocrine network that regulates cardiovascular and metabolic homeostasis.

5. *NPPA* variants in cardiovascular disease

NPPA variants are associated with plasma ANP concentrations, blood pressure levels and cardiovascular diseases (Lynch et al., 2009; Rubattu et al., 2014b). One of the variants, g.–664C>G, is in the 5' promoter region (Fig. 2). In a European population, the G allele was associated with low plasma ANP levels and high risks of hypertension and cardiac hypertrophy (Rubattu et al., 2006; Rubattu et al., 2007). A similar finding was reported in a Japanese population (Kato et al., 2000).

The variant rs5063, *i.e.* g.664G>A, is in *NPPA* exon 1, causing Val7Met substitution (Fig. 2). The variant did not appear to alter *NPPA* expression, as similar plasma ANP levels were found in individuals with the G and A alleles (Kato et al., 2000). The minor A allele was associated with low diastolic blood pressure (Zhang et al., 2005) and a low risk of hypertension (Conen et al., 2009; Conen et al., 2007). Conversely, the common G allele was linked to a high risk of cardiovascular disease (Lynch et al., 2008). In another study, however, the minor A allele predicted a high risk of stroke (Rubattu et al., 1999). In patients with familial hypercholesterolemia, the minor A allele was associated with lower levels of ApoA1 and HDL (Dedoussis et al., 2006).

The variant rs5065, *i.e.* g.2238T>C, is in *NPPA* exon 3 (Fig. 2), which alters the stop codon, creating a variant (ANP-RR) with two extra C-terminal Arg residues. This variant resembles ANP molecules in other mammalian sepiecs such as porcine, rat and mouse, which all contain two Arg residues at the C-terminus (Koller and Goeddel, 1992). The minor C allele was associated with high risks of hypertension (Niu, 2011), stroke (Rubattu et al., 2004), coronary artery disease (Barbato et al., 2012a), and myocardial infarction (Cannone et al., 2013b). In other studies, however, such an association was not confirmed (Kato et al., 2002; Lynch et al., 2008). More recent studies showed that the ANP-RR variant enhanced NPR-C signaling, causing endothelial dysfunction (Cannone et al., 2013b; Sciarretta et al., 2013) and oxidative stress in vascular smooth muscles (Rubattu et al., 2014a).

The variant rs5068, *i.e.* g.11905974A>G, is in the *NPPA* 3' untranslated region (Fig. 2). Individuals with the minor G allele had higher plasma ANP levels, lower systolic and diastolic blood pressures, and a reduced risk of hypertension, compared with those with two A alleles (Arora et al., 2013; Newton-Cheh et al., 2009). This minor G allele also predicted low risks of left ventricular hypertrophy (Arora et al., 2013; Newton-Cheh et al., 2009) and metabolic syndrome (Cannone et al., 2011; Cannone et al., 2013a). Apparently, the A to G

change abolished a binding site for microRNA-425 that inhibited *NPPA* mRNA expression in cardiac myocytes, which resulted in higher plasma ANP levels (Arora et al., 2013).

Atrial fibrillation (AF) is a common disease characterized by irregular heart rhythm. ANP deposits were reported in atrial amyloidosis, a pathological lesion linked to AF (Rocken et al., 2002). An *NPPA* frameshift mutation was reported in an AF patient family (Hodgson-Zingman et al., 2008). The mutation abolished the stop codon, adding 12 extra amino acids at the C-terminus of ANP (Fig. 2). The mutant ANP exhibited an enhanced biological activity and was more resistant to proteolytic degradation than wild-type ANP (Dickey et al., 2009; McKie et al., 2009). Patients with the mutation had elevated plasma ANP levels compared with that in normal controls (Hodgson-Zingman et al., 2008). It remains unclear how the mutant ANP contributed to AF in the patients.

6. ANP as a biomarker

The *NPPA* gene is up-regulated under physiological and pathological conditions. Mechanical stretch of the atrial wall is one of the most potent stimuli for ANP expression and release (Edwards et al., 1988). The signaling molecules in this process include integrins, p38 MAPK and focal adhesion kinase (Kerkela et al., 2011; Peng et al., 2008). To date, many growth factors and vasoactive molecules have been reported to enhance ANP expression and secretion (Ogawa and de Bold, 2014; Potter et al., 2006).

Peptide fragments derived from prepro-ANP have been detected in human plasma (Goetze et al., 2015). In population-based studies, elevated plasma NT-pro-ANP levels predicted the risk of cardiovascular events and death (Wang et al., 2004a). In an elderly European male population, high plasma ANP levels predicted the risk of AF (Mandalenakis et al., 2014). In patients with stroke, coronary artery disease, myocardial infarction and HF, elevated plasma NT-pro-ANP and ANP levels were associated with poor clinical outcomes (Barbato et al., 2012b; Makikallio et al., 2005; Sabatine et al., 2012; Volpe et al., 2010). These data indicate that ANP and related peptides are useful biomarkers in the diagnosis and risk stratification of cardiovascular diseases.

Most common methods to measure natriuretic peptide levels are immunoassays. Antibodies in these assays often have cross-reactivity between pro-ANP and its cleaved fragments (Xu-Cai and Wu, 2010). For example, antibodies against NT-pro-ANP are likely to recognize pro-ANP. Similarly, antibodies against ANP may bind to pro-ANP. As a result, an ANP assay may in fact measure both ANP and pro-ANP. Similar cross-reactivity has been reported for pro-BNP, NT-pro-BNP and BNP assays (Luckenbill et al., 2008). It is important, therefore, to consider the assay cross-reactivity when interpreting the data from these studies. A recent study showed that *NPPA* variants may alter the epitope recognized by the antibodies in the immunoassays, which may affect data analysis (Newton-Cheh et al., 2009).

7. ANP as a therapeutic agent

Given its unique pleiotropic functions in promoting natriuresis, diuresis and vasodilation and inhibiting aldosterone and renin secretion, ANP represents a promising drug candidate for

cardiovascular disease such as heart failure. In fact, a recombinant form of human ANP, carperitide, has been approved in Japan to treat HF patients (Mitaka et al., 2011; Saito, 2010). The peptide also showed therapeutic benefits in patients with myocardial infarction and kidney disease (Kasama et al., 2007; Kitakaze et al., 2007; Morikawa et al., 2009; Sezai et al., 2010). Because of its short plasma half-life (<5 minutes), carperitide is given by intravenous infusion. Currently, additional efforts are ongoing to develop ANP derivatives with improved pharmacological properties and therapeutic efficacies (Anker et al., 2015; de Bold et al., 2012; McKie et al., 2012; Zakeri and Burnett, 2011).

8. Conclusions

Since the discovery of ANP in the 1980s, we have gained considerable insights into the gene expression, biosynthesis, post-translational processing and biological function of this peptide hormone. In addition to its role in promoting natriuresis, diuresis and vasodilation, ANP also regulates cardiac function, vascular remodeling and energy metabolism. These functions are of significant importance in maintaining cardiovascular and metabolic homeostasis. To date, common *NPPA* variants have been identified that are associated with circulating ANP levels and hypertensive disease in the general population. Community-based studies indicate that plasma natriuretic peptide levels may be used to predict the risk of cardiovascular disease. The knowledge gained in understanding ANP biology has led to new therapies for heart disease. Currently, recombinant ANP is used as a parenteral drug to treat acute HF in patients. In recent clinical trials, a small molecule compound inhibiting the angiotensin II receptor type 1 and NEP, which degrades the natriuretic peptides, exhibited therapeutic benefits in HF patients (McMurray et al., 2014). These data indicate that enhancing natriuretic peptide activity can be used as a new therapeutic strategy for cardiovascular diseases. Further studies will be important to test if such a strategy may be extended to treat metabolic diseases.

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Abbreviations

AF	atrial fibrillation
ANF	atrial natriuretic factor
ANP	atrial natriuretic peptide
BNP	B-type or brain natriuretic peptide
cGMP	cyclic guanosine monophosphate
CNP	C-type natriuretic peptide

NEP	neutral endopeptidase
HF	heart failure
MAPK	mitogen-activated protein kinase
NPR-A	natriuretic peptide receptor A
NPR-C	natriuretic peptide receptor C
NT	N-terminal
PKG	cGMP-dependent protein kinase

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Highlights

- Atrial natriuretic peptide (ANP) is a hormone that regulates salt-water balance.
- ANP acts in the heart to prevent cardiac hypertrophy.
- ANP also regulates vascular remodeling and energy metabolism.
- ANP variants are associated with cardiovascular and metabolic diseases.

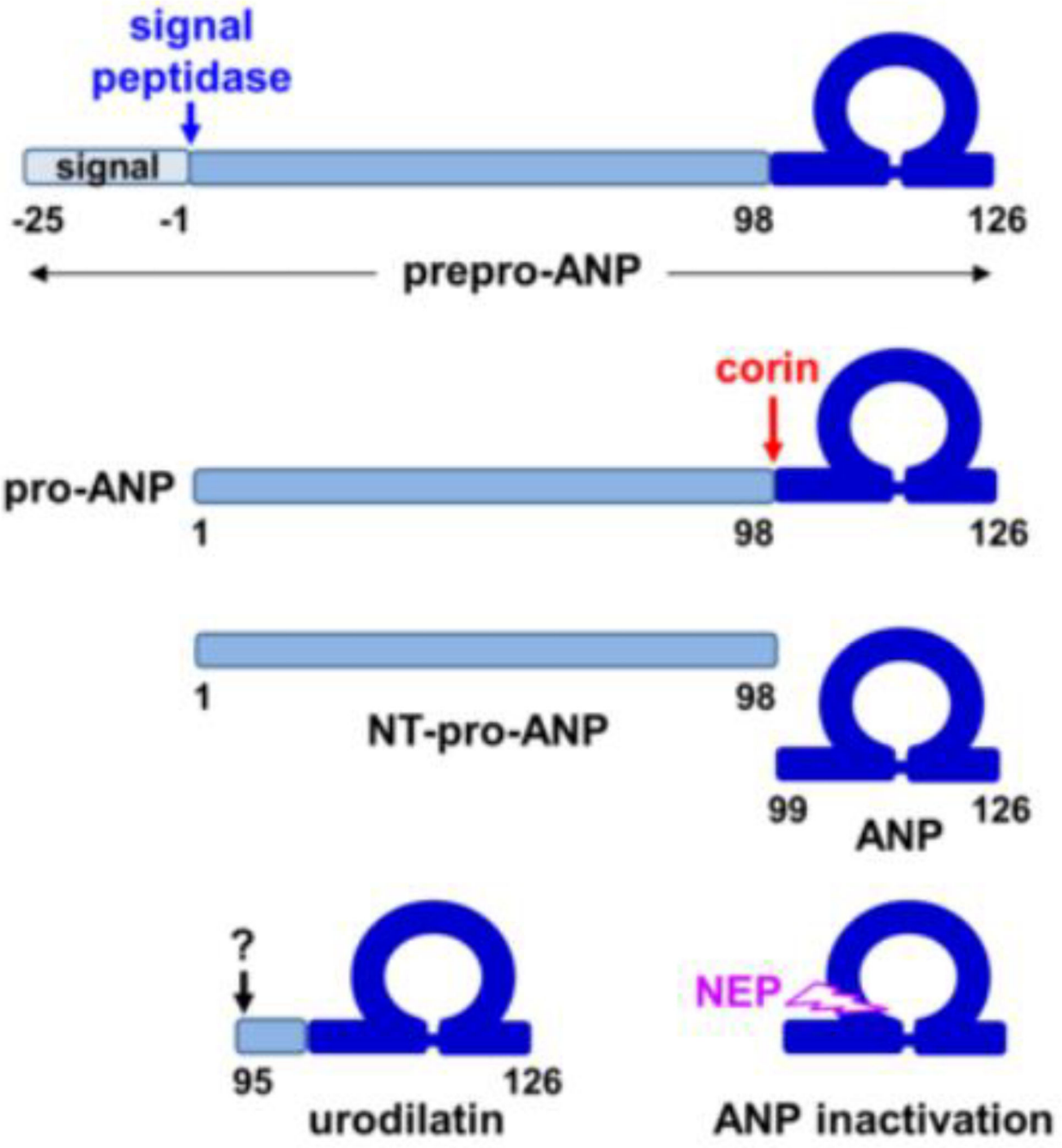

Fig. 1.

ANP synthesis and processing. ANP is synthesized as prepro-ANP. The signal peptide is removed by signal peptidase. Pro-ANP is converted to active ANP by corin. A disulfide bond connects two Cys residues, forming a ring structure in ANP. Neutral endopeptidase (NEP) inactivates ANP. In the kidney, alternative processing by an unknown enzyme generates urodilatin.

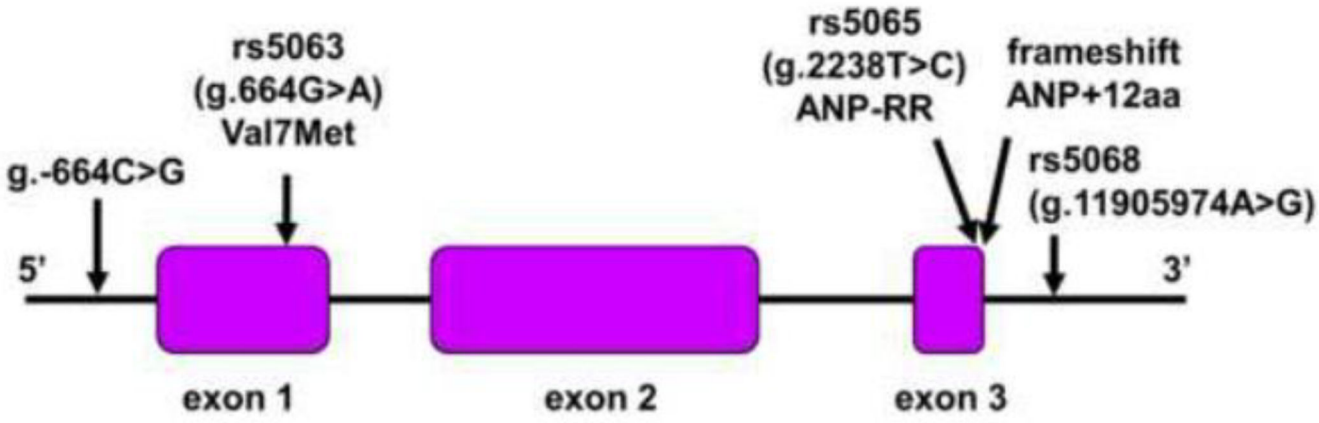

Fig. 2.

Variants and a frameshift mutation in *NPPA*. The human *NPPA* gene consists of three exons and two introns. *NPPA* variants in the 5' promoter region, exons 1 and 3, and the 3' untranslated region are indicated. A frameshift mutation abolishes the stop codon, creating a mutant ANP with 12 extra amino acids at the C-terminus (ANP+12aa).