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Current Cardiology Reviews, 2021, *17*, e051121191003

REVIEW ARTICLE

Atrial Natriuretic Peptide: Structure, Function, and Physiological Effects: A Narrative Review

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ARTICLE HISTORY

Received: October 21, 2020
Revised: December 08, 2020
Accepted: December 21, 2020

DOI:
10.2174/1573403X17666210202102210

Abstract: Atrial natriuretic peptide (ANP) is a cardiac peptide with multiple physiological effects, including natriuresis, blood pressure regulation, and renin-angiotensin-aldosterone system (RAAS) antagonism. Pre-proANP is synthesized in the atria and must be extensively cleaved by the protease corin to produce the mature 28 amino acid ANP. The downstream signaling pathway of ANP acts through the guanylyl cyclase receptor and the second messenger cGMP. Studies on ANP's physiological effects have demonstrated its activity on channels present in the apical membrane in the renal nephron, potentially inhibiting or decreasing sodium reabsorption. Recent research has also identified several clinical conditions, such as dilated cardiomyopathy, renal failure, and aging, associated with increased and decreased ANP levels. ANP levels could serve as a potential biomarker for the diagnosis of acute stages of heart failure, and ANP infusion could have a role in the management of acute or chronic heart failure.

Keywords: Atrial natriuretic peptide, corin, guanylyl cyclase receptor, cGMP, renin, hypertension, heart failure.

1. INTRODUCTION

Natriuretic peptides have been studied for several decades to understand their role in various physiologically important processes. Through several landmark experiments, the main natriuretic peptides have been identified and characterized. This review focuses on the atrial natriuretic peptide (ANP) and its structure and physiology in relation to renal and cardiovascular function.

2. CELLULAR ORIGIN AND STRUCTURE

Atrial natriuretic peptide (ANP) is released primarily from the cardiac atria and cleaved extensively before conversion to its metabolically active form [1-3]. Pre-proANP consists of 3 exons with 2 intervening introns, located on the short arm of chromosome 1. Its sequence has been studied by several investigators, including Flynn *et al*., and these investigators demonstrated that pre-proANP consists of a signal peptide-containing numerous hydrophobic residues that direct intracellular processing and trafficking [2, 4, 5]. Cleavage of the 152 amino acid sequence pre-proANP produces the 126 amino acid proANP, which is then cleaved by a transmembrane cardiac serine protease, corin, producing the 28 amino acid, biologically active molecule ANP [6, 7] (Fig. **1**). ProANP can also be alternatively cleaved by a different protease, resulting urodilatin, a 32-amino acid peptide [6]. The concentration of ANP in serum ranges from 25 to 60 pg/ml in normal subjects.

Atrial natriuretic peptide is released primarily in response to varying concentrations of electrolytes and water in the body and in response to stretch on the atrial wall due to increased volume [6, 8-11]. In 1979, De Bold and colleagues demonstrated that change in the number of atrial myocyte granules depends on the amounts of 2% NaCl and mineralocorticoids administered to rats [12]. Edwards *et al*. reported that increased atrial transmural pressure, which increases atrial stretch, causes more ANP release [8]. Thus, two factors that affect the amount of circulating ANP levels are the intravascular volume and solute concentrations.

3. PHYSIOLOGICAL EFFECTS ON THE KIDNEY

3.1. Renal Physiology

Several clinical conditions stimulate the release of ANP from the atria; these include volume overload and increased salt intake [10]. Rapid increases in systemic blood pressure stimulate the release of ANP, which lowers blood pressure and maintains cardiac function [10, 11]. Atrial natriuretic peptide dilates the afferent arteriole and simultaneously constricts the efferent arteriole of renal tubules. This mechanism increases the glomerular filtration rate (GFR), leading to increased urine excretion [10, 11]. The atrial natriuretic peptide also inhibits the reabsorption of sodium and water in renal tubules and inhibits renin secretion, further decreasing reabsorption and possibly antagonizing the sympathetic nervous system [11, 13-15]. Costanzo *et al*. and Guyton *et al*. concluded that stimulation of ANP by these various processes ultimately increases GFR and decreases systemic blood pressure [10, 11]. The specific physiological aspects are discussed below (Table **1**).

Research in the 1980s focused on ANP and its role in renal physiology. An infusion of alpha-ANP (50 µg bolus and then a continuous infusion) increases the GFR (+15%, P <

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0.05) and decreases diastolic blood pressure (-12%, P < 0.001) in healthy men under controlled conditions [16]. Sodium (+224%), chloride (+317%), magnesium (+110%), calcium (+158%), and phosphate (+88%) excretion rates were also significantly increased after ANP infusion even with an overall decrease in blood pressure [16]. These experiments help explain the various physiological effects of ANP on the kidney.

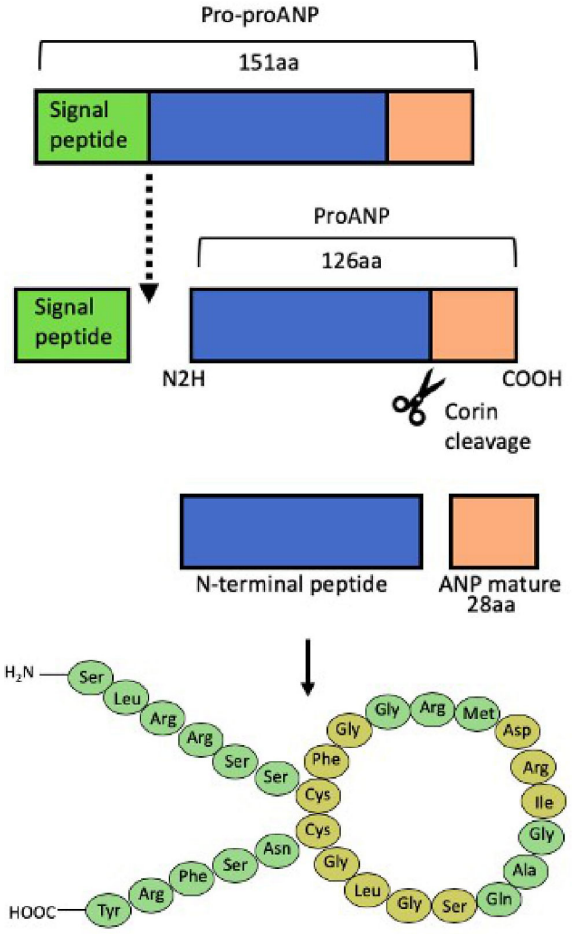

Fig. (1). Cleavage of pre-proANP and proANP/ANP structure. The 151amino acid pre-proANP, with a signal peptide with sequence rich hydrophobic residues, is cleaved by a signal peptidase to produce a 126 amino acid proANP [2]. The proANP is cleaved by corin, a transmembrane protease, to produce the 28 amino acid active ANP and an N-terminal peptide. A disulfide bridge is present between the two cysteine residues [position 7 and 23] in active ANP [6, 17]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.2. Subsection 1 - Corin

The ANP pathway involves proteases, receptors, and signaling, which have specific physiological effects on the kidney. Corin is a transmembrane serine protease that cleaves pro-ANP to generate functional ANP [6, 17]. This protease was discovered and isolated by Yan *et al*. and is a polypeptide composed of 1042 amino acids with an approximate mass of 116 kDa [18]. Through the use of a cDNA probe to detect its expression in specific tissues, researchers localized most corin expression in human cardiac tissue; corin mRNA was also present in other tissues, such as the kidney and uterus, in mice [18]. After discovering corin in 1999, Yan *et al*. and others confirmed the role of corin in ANP processing and established its highly sequence-specific proteolytic activity [7].

Corin has an essential role in ANP processing and indirectly in blood pressure regulation. Corin knockout mice, generated by the deletion of exon 19 in the murine corin gene, have a 2.6-fold increase in pro-ANP levels and undetectable ANP levels, confirming the role of corin in ANP processing [19, 20]. Corin knockout mice also have increased blood pressures compared to wild type mice [20]. Blood pressures in knockout mice were 120 ± 3 mmHg in males and 119 ± 2 mmHg in females; in the wild type mice, blood pressures were 109 ± 4 mmHg in males and 112 ± 1 mmHg in females [20]. Additional experiments with a rat model with proteinuric renal disease reported decreased basal levels of corin and increased ENaC expression, which suggest a correlation between corin levels and its potential involvement in kidney disease [21].

Table 1. ANP physiological effects.

Location	Physiological Effect
Heart	Anti-hypertrophic function
Kidney	Dilation of renal afferent arteriole Constriction of renal efferent arteriole Increased glomerular filtration rate (GFR) Inhibition of Na^+ and H_2O reabsorption Possible inhibition of renin & aldosterone release Increased natriuresis/diuresis
Blood Vessels	Increased capillary permeability Vasodilation
Systemic	Decreased systemic blood pressure Decreased blood volume
Nervous System	Decreased sympathetic nervous system activity
Molecular and Second Messenger Activity	Increased GTP conversion to cGMP through NPR Increased production of NO Downstream activity to produce physiological effects mentioned above

Abbreviations: GMP-guanosine monophosphate; GTP-guanosine triphosphate; NO-nitric oxide.

The primary site of corin synthesis is in cardiac myocytes, but it has also been found in other tissues, particularly in human renal segments [21-24]. Dong *et al*. discovered a marked difference in corin distribution; the proximal convoluted tubule (PCT) had higher levels than the distal convoluted tubule (DCT) and collecting duct with relative optical densities of 0.16 ± 0.01, 0.10 ± 0.01, and 0.07 ± 0.02, respectively [22]. Corin expression correlated with the expression of ANP and natriuretic peptide receptor A (NPR-A), which were strongly stained in the PCT [22]. This pattern and proximity suggest co-dependency of these factors in renal sodium reabsorption and the regulation of blood pressure levels to achieve homeostasis. However, an earlier study by

Polzin *et al*. presented different results with respect to corin location in rats, and the PCT had corin expression but low levels of ANP protein despite a correlation between corin and ANP mRNA expression [21]. This discrepancy may be explained by different experimental methods or by biological differences in human and rat kidney corin and ANP expression and indicates the need for additional experiments on corin/pro-ANP/ANP in both animal models and human subjects.

3.3. Subsection 2 – cGMP/Guanylyl Cyclase

The guanylyl cyclase (GC)/cGMP signaling pathway has an essential role in amplifying downstream ANP effects. Weil *et al*. studied the link between increased ANP and cGMP levels. Patients were infused with saline to cause volume overload; ANP levels were increased 2.5-fold and cGMP levels were increased almost 3-fold when compared to basal levels [25]. In other experiments, mice with GC-A deletions or gene knockout developed cardiac hypertrophy and impaired cardiac function, such as reduced left ventricular contractility [26, 27]. The cardiomyocyte area and blood pressure levels were 6.05 ± 0.26 mm^2/g weight and 122 ± 3.4 mmHg, respectively, in knockout mice, and 5.15 ± 0.14 mm^2/g weight and 94 ± 4.5 mmHg, respectively, in wild type mice [26]. However, Holtwick *et al*., surprisingly, reported hypotension and enhanced expression of hypertrophy markers in GC-A knockout mice [27]. To understand the physiology and mechanism of the concurrent increases, the structure and function of the guanylyl cyclase receptor must be considered.

Guanylyl cyclase receptors are transmembrane receptors with an extracellular ligand-binding domain and a catalytic domain (Fig. **2**) [28, 29]. The atrial natriuretic peptide was found to bind to these receptors in experiments in which guanylyl cyclase-A null mice failed to regulate blood pressure despite having normal levels of ANP [30]. Guanylyl cyclase receptors have other domains, but the catalytic domain is the most important since it converts GTP to cyclic GMP [28, 31]. When ANP binds to the guanylyl cyclase receptor, an extracellular portion of the receptor is cleaved, inducing a conformational change [32]. After the binding of ANP to NPR-A, a guanylyl cyclase receptor, GTP is converted to cGMP, producing downstream effects through a signaling cascade. This pathway ultimately decreases blood pressure and promotes natriuresis [10, 11, 28, 29, 31, 32].

3.4. Inhibition of Renin Release

One proposed downstream effect of ANP is the inhibition of renin release from the juxtaglomerular (JG) cells. Renin is produced by JG cells and is a key component of the renin-angiotensin-aldosterone system (RAAS), which promotes salt reabsorption and increases blood pressure [10]. Cultured rat kidney JG cells stained with immunofluorescent dye demonstrated the potential inhibitory effect of ANP on renin release since decreased renin release from JG cells was observed as ANP levels were increased. This result was also accompanied by a marked increase in cGMP levels as ANP levels increased [14]. Scriven *et al*. demonstrated the same correlation between ANP and renin through inferior vena cava balloon inflation and synthetic ANP injection in healthy

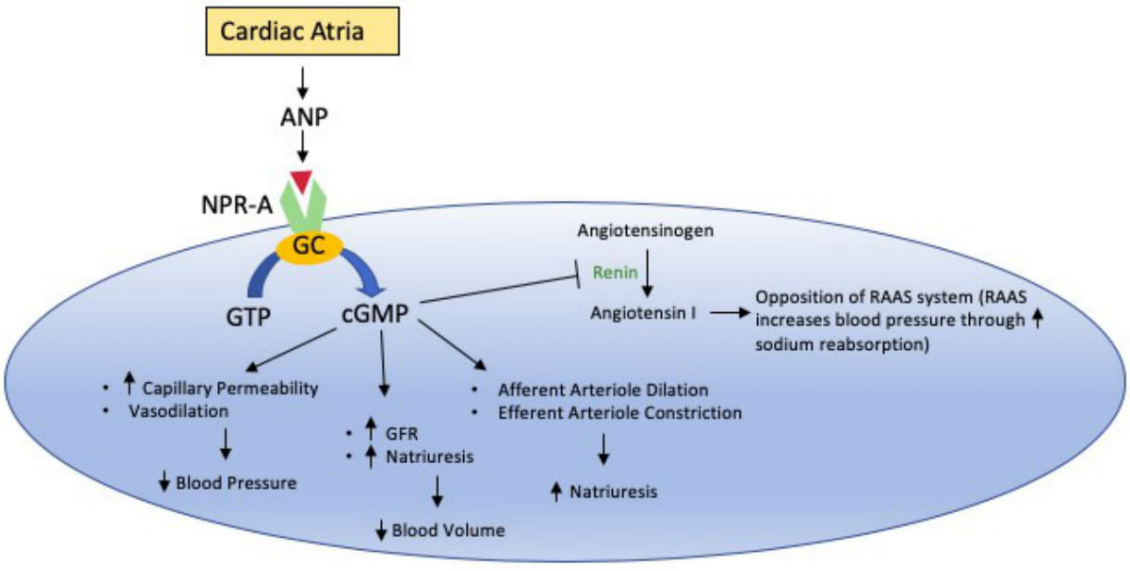

Fig. (2). Downstream effects of ANP and cGMP. ANP binds to natriuretic peptide receptor A, a guanylyl cyclase receptor, converting GTP into cGMP. Then cGMP induces effects, such as vasodilation and increased natriuresis, to reduce systemic blood pressure. cGMP may also alter the effects of RAAS and the sympathetic nervous system [10, 11]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

anesthetized dogs and in dogs with acute low output heart failure. The control group and experimental group showed significantly decreased renin secretion. Renin secretion in the control group decreased from 308.5 ± 84.5 ng/min to 44.5 ± 27.5 ng/min, and in the acute low-output heart failure group, renin secretion decreased from 852.8 ± 183.0 ng/min to 149.5 ± 73.7 ng/min [15]. Opgenorth *et al*. infused ANP in normal dogs and in dogs with non-filtering kidneys to show that increased sodium delivery to the macula densa was responsible for the decreased renin release; renin secretion decreased from 325.5 ± 87.4 ng/ml to 52.4 ± 29.4 ng/ml in dogs with intact kidneys, while dogs with non-filtering kidneys did not have the same inhibition of renin release [33].

However, there has been controversy about whether ANP directly inhibits renin release, and some experiments have shown that ANP has no effect on renin release [34, 35]. This discrepancy may be due to different cell culture incubation protocols, different purification methods for JG cells, or different animal models used [34]. In addition, while current research has definitely demonstrated a possible relationship between ANP and renin, elucidation of the exact mechanism in humans will require more studies.

4. RENAL NEPHRON CHANNEL EFFECT

Atrial natriuretic peptide has an effect on several channels in the renal nephron. Specific channels are present in different parts of the nephron, and they contribute to sodium regulation through various effector mechanisms [10]. The location of these channels can be categorized into specific regions of the nephron: the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct [10, 11]. This section discusses the downstream effects of ANP on the proximal tubule, the loop of Henle, and the collecting duct.

4.1. Proximal Tubule

In the proximal tubule, the Na^+/H^+ cotransporter is present on the apical cell membrane, and the Na^+/K^+ ATPase cotransporter is located on the basolateral cell membrane. With approximately 80% of filtered sodium absorbed in this location, the proximal convoluted tubule is a major site for the regulation of sodium reabsorption [36]. Experiments with rabbits demonstrated that ANP inhibits Na^+/H^+ ATPase indirectly by increasing the intrarenal generation of dopamine, which inhibits the Na^+/H^+ ATPase [37]. The Na^+/K^+ ATPase located on the basolateral membrane was not inhibited by ANP in the proximal tubule [36, 38]. However, ANP eliminated the stimulatory effects of angiotensin II on Na^+/K^+ ATPase activity [36]. Beltowski *et al*. demonstrated that ANP infusion in rats did not affect the Na^+/K^+ ATPase activity in the cortex, its location in the PCT, but did cause dose-dependent inhibition of Na^+/K^+ ATPase cotransporters in the medulla [39].

4.2. Loop of Henle

Sodium absorption in the thick ascending loop of Henle is mediated through the $Na^+/K^+/2Cl^-$ transporter (NKCC2) located in the apical cell membrane. Various experiments have examined the effects of ANP on NKCC2 and the effects of cGMP on NKCC2. Ortiz *et al*. demonstrated the natriuretic effects of nitric oxide (NO) through L-arginine stimulation and the subsequent increase in cGMP levels with multiple steps leading to the eventual decrease in cAMP levels and decreased sodium absorption. Moreover, chloride absorption was decreased by 35.2% [40]. This sequential effect of NO was evident when inhibition of guanylyl cyclase failed to inhibit sodium absorption in the presence of NO [40, 41]. Nitric oxide activates the guanylyl cyclase receptor and increases cGMP levels, which inhibits sodium absorption [40]. While experiments have shown increases and decreases in the levels of the various factors, the exact mechanism is still not completely understood. The assumption is that ANP mediates the downstream effect of increased cGMP levels, indirectly leading to greater NO production and a subsequent reduction in blood pressure. Currently, there are no data that describe the function of these factors in a specific sequence.

4.3. Collecting Duct

The apical cell membrane of the collecting duct has the Epithelial Na^+ channels (ENaC) and the Aquaporin 2 channels (AQ2), which promote sodium and water reabsorption. Research conducted on the physiological effects of ANP on the collecting duct is sparse compared to that on other parts of the nephron. It is known that ANP promotes diuresis and urine excretion [10, 11, 42]. In an additional experiment, ANP, with the involvement of NPR-A, decreased the activity of ENaCs present on the apical cell membrane of the collecting duct, possibly in a cGMP-dependent manner in *Xenopus laevis*, the African clawed frog, distal nephron epithelial cells [42]. The AQP2 channel, through the regulation of anti-diuretic hormone, is localized to the apical cell membrane during experiments with low blood pressures [10]. In a different study reported by Wang *et al*., ANP infusion in rats did not lead to a change in channel localization initially but did increase the localization of the AQP2 and ENaC channels after 90 minutes of prolonged ANP infusion [43]. The effect of ANP on AQP2 was also studied in relation to vasopressin, which has the opposite effect in tubules. Klokkers *et al*. demonstrated a decrease in AQP2 localization, *i.e.*, insertion, with ANP after vasopressin infusion and no AQP2 localization when ANP was the only stimulant [44]. The same experiment also showed an increase in cGMP levels after ANP infusion from 1.3 ± 0.3 to 107.1 ± 5.6 pM/well [44].

In summary, ANP inhibits the Na^+/H^+ cotransporter located in the apical cell membrane in the proximal tubules during dopamine administration. In some experiments, ANP also indirectly inhibits the Na^+/K^+ ATPase located on the basolateral cell membrane of the PCT. In the Loop of Henle, ANP may mediate the downstream effect of increased cGMP levels, indirectly leading to greater NO production and a subsequent reduction in blood pressure through actions of the NKCC2 channel; however, specific mechanistic experimental data are sparse. In the collecting duct, ANP decreases ENaC activity and potentially decreases AQP2 channel localization to the apical cell membrane (Fig. **3**).

5. ANP LEVELS IN CLINICAL DISORDERS

5.1. Increased Levels

Several cardiac and renal diseases have changes in ANP plasma levels. Increased ANP levels have been associated with dilated cardiomyopathy (DCM), hypertension, tachyarrhythmias, and chronic renal failure [45-48]. Cardiac diseases that increase the preload and afterload of the atria and/or ventricles often lead to compensatory decreases in the blood pressure that might be mediated in part by ANP [10]. Saito *et al*. reported a 40-fold increase in ANP mRNA levels in the ventricles of adults with DCM and a 55-fold increase in ventricular ANP levels, from 0.02 µg/g in the control group to 1 µg/g in the DCM group [45]. A subsequent experiment with spontaneously hypertensive rats yielded similar results, with a marked decrease in the left atrial ANP to ANP mRNA ratio in hypertensive rats, suggesting increased ANP secretion associated with this condition [46]. These experiments suggest that ANP is secreted rapidly from cardiac tissue to compensate for ventricular wall stress [45, 46]. Recent experiments have produced similar results with a slightly more comprehensive understanding of mechanistic actions. Witthaut *et al*. demonstrated an increase in plasma ANP levels in septic shock patients compared to that in control subjects [82.7 ± 9.9 pg/ml *vs* 14.9 ± 1.2 pg/ml] [49]. In addition, increases in ANP in pediatric patients with congenital heart disease associated with heart failure occur, with the highest ANP levels measured in patients with DCM [50].

Experiments measuring ANP levels in both rats and humans have shown an association between age and ANP [51-56]. Pollack *et al*. conducted experiments with a rat model and found no significant difference in plasma ANP secretion rates during volume expansion in the old and young rat groups [52]. When these rats were stimulated by atrial stretch or with endothelin, both groups had increased ANP secretion rates. However, younger rats had a bigger increase in ANP secretion after atrial stretch (mechanical stimulation) and a bigger increase after endothelin (a receptor mediated stimulus). Pollack *et al*. attributed this discrepancy to the anesthesia used with these animals, which may have normalized cardiac pressure [52]. The reason for the correlation between age and ANP might also be explained by aging causing increased volume overload, thereby leading to increased ANP secretion but decreased reserve if needed for an acute compensatory response. However, it is unclear whether increased ANP levels in older patients have negative consequences and possibly contribute to some cardiac and renal diseases seen with older age.

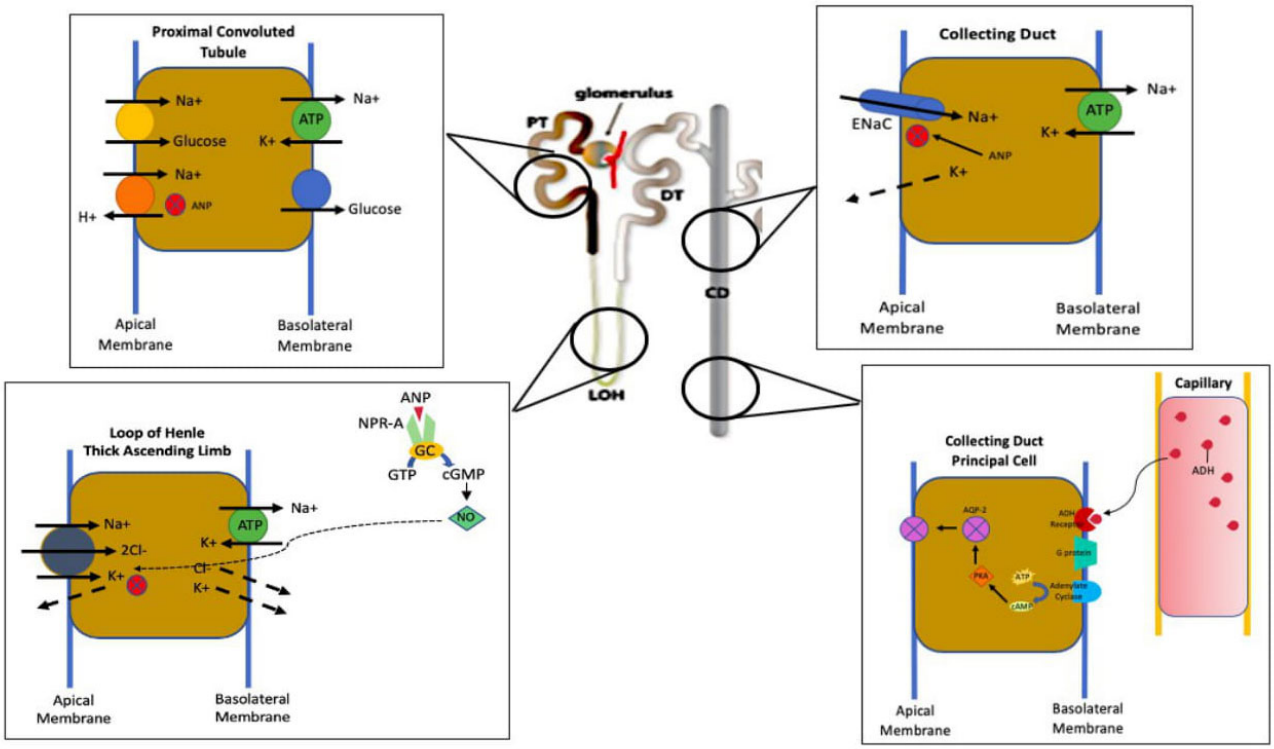

Fig. (3). Channels present in parts of the nephron [95]. In the PCT, the Na^+/H^+ ATPase is inhibited by ANP [37]. The second messenger cGMP induces the production of NO, inhibiting NKCC in the TAL LOH [40, 41]. The collecting duct has the ENaC channel; ANP may decrease the translocation of these channels and prevent sodium reabsorption [42]. Principal cells in the collecting duct exhibit decreased AQP2 expression on the apical membrane in the presence of ANP after ADH administration [43, 44]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.2. Decreased Levels

Decreased ANP levels have been found in several disorders. Patients presenting with decompensated heart failure had 7.6-fold lower levels of corin with higher levels of proANP than the control group, suggesting that reduced corin cleavage contributes to the exacerbation of heart failure [57]. This result differs from research linking an increase in ANP to other cardiac diseases [45-48]; however, in comparison to other conditions, heart failure may be more acute and have different pathophysiological associations with ANP. Patients with hypertension presented with decreased levels of proANP in the prehypertension stage and a failure to increase ANP levels in various hypertensive stages, suggesting a defect in the release of ANP in hypertension [58]. Since the molecular mechanisms are not known, activation of other compensatory systems, such as RAAS or the sympathetic nervous system, may be involved in the decreased expression of ANP [10, 11, 59]. The lack of research on the causes of low ANP levels indicates the need for more studies in relevant clinical diagnoses.

One approach to examining ANP levels requires the use of well-defined study populations, with attention given to age and gender. Hamada *et al*. found higher ANP levels in women than in men and found a positive correlation between age and ANP levels [60]. These results demonstrate the need to determine baseline ANP levels based on patient characteristics in the study and then consider possible differences in ANP levels in a particular clinical disorder.

6. DIAGNOSIS OF HEART FAILURE

Heart disease is the leading cause of death in the United States [61]. In congestive heart failure (CHF), ANP levels have some value in the diagnosis of different stages. Measurement of plasma ANP in patients with CHF found increased levels of ANP compared to healthy controls [59, 62-64]. Studies correlating the severity of heart failure and ANP mRNA/ANP and brain natriuretic peptide (BNP) mRNA/BNP levels demonstrated that ANP levels are a better indicator of acute heart failure rather than they are in chronic heart failure [59, 62, 65]. This was based on a 3-fold increase in ANP plasma levels in the initial stages of heart failure (acute) with a plateau in ANP mRNA expression as the disease progressed into a more chronic stage [65]. In addition, Langenickel *et al*. found increased left ventricular ANP mRNA expression in rats with small shunts (equivalent to acute HF) in contrast to increased left ventricular BNP mRNA expression in rats with large shunts (equivalent to chronic HF) [65]. Patients with chronic heart failure have greater increases in BNP levels [65]. The same pattern of ANP and BNP levels was shown with decompensated versus compensated heart failure in experiments with canine hearts [66]. Cowie *et al*. hypothesized that N-terminal ANP and BNP might have better utility than ANP as diagnostic tests. However, experiments measuring all three in ventricular dysfunction found BNP was the most sensitive and predictive, emphasizing the need for cut-off values for both ANP and BNP in diagnostic tests [64].

One factor contributing to the increased release of ANP in heart failure is myocardial stretch [59, 63]. As the heart muscle deteriorates in HF, cardiac output is dramatically decreased, causing activation of the RAAS system and sympathetic system and subsequently increasing blood pressure. This deterioration can also induce hypertrophy of the left ventricle due to increased afterload. ANP is released to counterbalance cardiac pressure elevation and stretch, inhibit RAAS, and induce diuresis [10, 59]. However, studies on the correlation between ANP/BNP levels and diastolic function have not consistently predicted cardiac function [67, 68].

The increase in ANP levels observed in patients presenting with heart failure should lead to a decrease in preload, resulting in some level of compensation. However, this effect is not always seen in HF patients. What factors block the compensatory effect of ANP? One hypothesis involves the downregulation of ANP receptors [69-72]. Tsutamoto *et al*. demonstrated this possibility indirectly by measuring cGMP and ANP levels in two groups of HF patients. A positive correlation was seen between cGMP and ANP levels in the group with less severe HF, but no correlation was found in the severe HF group, with plasma cGMP levels leveling off as ANP levels increased [70]. Tsunoda *et al*. reported similar results with a decreased density of ANP receptors in the inner medulla of rats in a more severe myocardial infarction group [71]. These observations suggest the downregulation of ANP receptors in more severe HF, perhaps contributing to a decreased compensatory effect.

Another possible reason for this decreased effect is the saturation of ANP receptors; however, experiments conducted to measure receptor affinity proved this explanation unlikely [69, 71]. An experimental study with heart failure patients found ANP suppression of RAAS in early or less severe HF and an increase in RAAS activity in chronic HF [13]. Since ANP release suppresses the RAAS to some extent, another possible mechanism could be the increased stimulation of the RAAS and sympathetic system by other pathways or through ANP regulating itself [71, 72]. Yechieli *et al*. reported increased plasma aldosterone levels with increased ANP levels [72]. There may be other hormones involved in more severe HF that affect the ANP receptor density. While these are several potential hypotheses, the exact mechanism remains unknown.

7. ANP MIMETICS AND THE MANAGEMENT OF HEART FAILURE

Several ANP mimetics have been developed, and these decrease blood pressure, promote diuresis and natriuresis, and have other physiological effects related to their differences in structure from endogenous ANP [73]. The ANP mimetics studied include mini-ANP, vasonatrin, and ANP analogs with increased affinity to NPR-A [74-78]. The structures and effects are described in Table **2**.

To increase the pharmacological effects of ANP, BNP, and mimetics, inhibitors of the enzyme neutral endopeptidase were developed. Neutral endopeptidase inactivates neu-

Table 2. ANP mimetics produce similar physiologic effects.

Category	Substance	Molecular Structure	Action
ANP Mimetic	mini-ANP	15aa: epitope placed on Cys^{7}-Cys^{23} ring [73]	Biological activity and affinity to the ANP-A receptor but demonstrated less potency than native ANP
-	Vasonatrin	C-terminal peptide from ANP attached to CNP [73]	Promoted natriuresis Demonstrated intermediate potency when compared to ANP and CNP Increased arterial venodilation to a greater extent than ANP and CNP alone [potentially related to degradation pathway differences]
-	NPR-A higher affinity ANP analogs	ANP analogs created from phage display libraries [73]	Increased affinity for the NPR-A receptor versus the NPR-C receptor Demonstrated natriuresis Relaxation of cardiac aortic rings
NEP Inhibitor	Candoxatril	2,3-dihydro-1H-inden-5-yl ester of candoxatrilat's enantiomer [90]	Increased levels of plasma ANP Increased Na^{+} and H2O excretion No significant decrease in systemic blood pressure
-	Sinorphan	S-enantiomer of Acetorphan [91]	Did not effectively reduce CHF symptoms Adverse effects present, including aplastic anemia
-	Acetorphan	Lipophilic thiorphan prodrug [92]	Increased ANP-like immunoreactivity (same phrase in the paper) Increased urinary output volume
Vasopeptidase Inhibitor	Lisinopril	Dipeptide [93]	Decreased blood pressure when administered with a NEP inhibitor [candoxatril, sinorphan]
-	Omepatrilat	Dipeptide [94]	Decreased blood pressure Potentially beneficial in CHF patients Decreased rate of renal dysfunction Adverse side effect: Angio-edema
-	MDL 100,240	-	Decreased blood pressure Increased natriuresis and diuresis
-	Sampatrilat	-	Decreased systolic and diastolic blood pressure Increased urinary cGMP

ropeptides, and these inhibitors (NEPI) could have important pharmacological effects [79]. Similarly, due to the antagonistic effects seen on the angiotensin II and the RAAS system after increased natriuretic peptide levels, inhibitors for the angiotensin-converting enzyme were developed and combined with NEPI, termed vasopeptidase inhibitors (VPI), and these drugs produced better results in patients with hypertension and CHF [73]. However, serious side-effects have occurred with these drugs [73, 74]. The structures and functions for NEPIs and VPIs are listed in Table **2**.

ANP has proven useful in the diagnosis of cardiac disorders and may also be useful in the management and treatment of heart failure. Several studies using ANP injections have demonstrated important hemodynamic effects, including decreased pulmonary capillary wedge pressure (PCWP), decreased total systemic resistance, and significantly lowered right atrial pressure [59, 80-87, 89]. Infusions of ANP in patients with CHF have also reduced aldosterone levels, suggesting suppression of the antagonistic effect of RAAS [80, 81]. However, these changes were not significant, and the suppression did not persist throughout the ANP infusion protocol; in addition, other studies found no change in renin or aldosterone levels after human ANP and urodilatin administration [83, 88]. These differences in effects, specifically on the RAAS, may be due to differences at the molecular level since urodilatin is alternatively processed from pro-ANP [86, 89].

The reduction in total systemic resistance observed with ANP infusion is potentially beneficial for patients with CHF since total systemic resistance reflects afterload and modulates left ventricular pressure [10, 11, 80]. A significant decrease in pulmonary artery pressure and an increase in cardiac output have been observed in clinical studies, contributing to overall reductions in pressure and volume overload normally seen in patients with CHF [80, 81, 83, 84, 87]. A potential issue, however, may arise due to differences in clinical studies and injection boluses, possibly contributing to the reported discrepancies. Although the experiments discussed demonstrate beneficial effects with ANP infusions, a set of standardized doses would facilitate comparisons of physiological effects seen in different clinical studies.

Recent clinical trials have measured ANP levels in patients with acute heart failure and the effect of synthetic ANP in these patients. Matsumoto *et al*. measured serum levels of ANP in 113 patients with acute heart failure [90]. Patients were divided into 2 groups: heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. The patients then received carperitide (a synthetic α human A-type natriuretic peptide) for 6 hours and di-

uretic effects were measured. Patients with preserved ejection fractions had lower levels of ANP and BNP. Patients with low baseline ANP levels had better responses to exogenous ANP based on urine output over 6 hours. In addition, patients with preserved ejection fractions and patients with atrial fibrillation had higher urine outputs over 6 hours. This study suggests that ANP deficiency may identify patients who will respond to exogenous ANP with more diuresis. This might provide important benefits during the initial phase of hospitalization in patients with acute heart failure. Murphy and coworkers measured serial ANP levels in 144 patients with heart failure with reduced ejection fractions, and treated the patients with sacubitril/valsartan [91]. There was a significant increase in ANP at day 14 with further increases through day 45. This increase in ANP was followed by an increase in urinary cyclic guanosine phosphate excretion and improvement in left ventricular ejection fraction (30.9% [baseline] to 35.6% [6 months] to 41.6% [12 months]) and left atrial volume index (34.8 ml /m^2 [baseline] to 30.4ml/m^2 [6 months] to 27.2 ml/m^2 [12 months]). This study suggests that increases in ANP levels explains part of the benefits with this drug combination which includes a neprilysin inhibitor which should reduce the metabolism of ANP. However, Matsue *et al*. retrospectively reviewed the outcomes in patients with acute heart failure requiring hospitalization [92]. Patients treated with carperitide were matched with similar patients who was not were not treated with this drug using propensity scoring. Patients treated with carperitide had an increased odds of in-hospital mortality (2.13; 95% CI:1.17-3.85). Patients younger than 75 had better responses to this drug. This study demonstrates that this drug needs to be studied in well-designed, randomized, placebo controlled clinical trials.

One point of uncertainty is the minimal effect ANP infusion has on diuresis in patients with CHF. While ANP increased diuresis and sodium excretion in the control group (without CHF), it may not produce significant increases in diuresis in CHF patients [80-83]. However, injection with urodilatin [ANP 95-126] was more effective in increasing natriuresis [88]. This outcome could be due to a slower elimination or inactivation rate, but the exact reason for this has not been determined [86, 88]. Although ANP infusion may have important pharmacological effects, some side effects have been associated with it. A small number of patients treated with ANP reported hypotension, syncope, and vomiting, which required discontinuing the infusion and saline administration to reverse these side effects [81, 82].

The exact role of natriuretic peptides in the treatment of patients with heart failure remains unclear. A large study with BNP illustrates this problem. O'Connor *et al*. studied 7,141 patients hospitalized with acute heart failure [93]. They were randomized to either nesiritide or placebo for 24 to 48 hours. Patients on nesiritide had an improved dyspnea at 6 and 24 hours, but the prespecified level of significance was not met. There were no differences in the rates of rehospitalization or death for any cause within 30 days between the 2 groups. There was no significant difference in changes in renal function in the 2 groups. Patients receiving nesiritide did have an increased frequency of asymptomatic and symptomatic hypotension. This study highlights the need for well-designed clinical trials in patients with acute heart failure requiring hospitalization. Important factors include prespecified clinically relevant study goals and careful attention to possible side effects, including hypotension, renal dysfunction, rehospitalization, and death. The use of ANP in patients was heart failure requires longitudinal studies to measure ANP levels in patients with both acute and chronic heart failure. The initial course in patients with chronic disease is likely characterized by increased ANP levels. However, over time, a chronic course may be associated with decreased levels or "ANP deficiency". This information would potentially identify patients who would benefit from the infusion of ANP or ANP mimics. In addition, the use of these medications requires rapid laboratory measurements, possibly with point-of-care technology.

CONCLUSION

The main physiological effect of ANP is the reduction in blood pressure through diuresis. Cleavage of proANP by corin, a transmembrane serine protease, is an essential step in the formation of ANP, which then produces a variety of downstream effects through cGMP. These regulatory effects vary in different zones of the renal tubules. These effects, such as natriuresis, occur in patients with CHF, hypertension, and chronic renal failure and correlate with increased or decreased ANP levels found in these conditions. ANP has a clinical role in heart failure management and diagnosis. It can serve as a key marker for early acute heart failure; increased levels of BNP can serve as the marker for more chronic stages, suggesting the need to monitor and to measure both peptides as diagnostic tools. Since ANP has several important functions in normal physiology and in several clinical disorders, more study is needed to better understand its mechanisms and its possible role in the management of CHF.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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