REVIEW

Cardiovascular Therapeutics

Cardiac Natriuretic Peptides: From Basic Discovery to Clinical Practice

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Anaritide; ANP; BNP; Cardiac transcription factors; CNP; Congenital heart defects; Gene regulation; GATA4; Heart failure; Natriuretic peptides; Nesiritide; NKX2.5; TBX5.

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Discoveries of the cardiac natriuretic peptides ANP, BNP, and CNP along with studies of their function and regulation in health and disease, have led to breakthroughs in the understanding and clinical management of heart failure. Analysis of the ANP and BNP promoters and patterns of expression uncovered a set of key regulators and pathways that converge onto these sensitive markers of early myocyte differentiation and cardiac stress. Among the most studied are the transcription factors GATA4, TBX5, and NKX2—5, which are central to cardiac development and mutations of which are associated with congenital heart disease. In clinical practice, plasma natriuretic peptides levels have been used as quantitative biomarkers of heart failure and proved to be highly effective for the diagnosis of heart failure, for risk-stratification of patients and guided therapy, as well as for screening for subclinical cardiac stress. Emerging studies are revealing the cardioprotective attributes of these peptides and may offer new therapeutic venues for myocardial infarction and heart failure. Clinical trials have documented the benefits and risks of the use of synthetic ANP (Anaritide) and BNP (Nesiritide) for treating heart failure, renal failure, and hypertension. This review summarizes the function and regulation of cardiac natriuretic peptides and the translation of the basic biochemical discoveries into clinical practice both at the diagnostic and therapeutic level.

Introduction

The landmark discovery of atrial natriuretic peptide (ANP) in 1981 by de Bold [1] and its expression in the ventricles by Nemer et al. [2], followed by the characterization of brain or B-Type natriuretic peptide (BNP) [3] are commonly associated with breakthroughs in cardiovascular endocrinology and innovations in the diagnosis of heart failure. They have not only provided diagnostic and therapeutic tools for clinicians but have contributed greatly to our current understanding of cardiac development. A third member of this family, C-Type natriuretic peptide (CNP) [4], initially thought to be restricted to the vasculature but also produced by the heart [5], has recently been attributed cardioprotective properties [6,7]. At the genetic level, analysis of the ANP and BNP promoters and patterns of expression have led to the characterization of a set of key regulators and pathways that converge onto these sensitive markers of cardiac stress. Among the most studied are the transcription factors GATA4, TBX5, and NKX2—5, which are central to cardiac development and mutations of which were found to be associated with cardiac defects [8]. In clinical practice, natriuretic peptides levels have been used as quantitative biomarkers of heart failure; measuring their plasma levels has allowed accurate diagnosis of heart failure, risk-stratification of patients and guided therapy, as well as screening for subclinical cardiac disease. Clinical trials have documented the benefits and risks of the use of synthetic ANP (Anaritide) and BNP (Nesiritide) for treating heart failure, renal failure, and hypertension [9–11]. This review summarizes the current knowledge on cardiac natriuretic peptides with emphasis on their expanding roles in diagnosis, therapeutics, and in elucidating the molecular mechanisms and pathways underlying heart disease.

Biochemistry

ANP was initially isolated from atria (hence its name) and in the postnatal heart, the atria are the primary site of ANP expression [12]. During embryonic development, ANP is also expressed at high level in the left ventricle, but this expression falls precipitously after birth to mRNA concentrations 100-fold lower in adult ventricle versus atria [2]. Other tissues express ANP in albeit much lower quantities such as the pituitary, lungs, hypothalamus, and kidneys [13,14]. ANP is synthesized within atrial cardiomyocytes as a 151 amino acid peptide and stored as proANF (126 amino acid residues) into specific granules. Its biologically active form of 28 residues [13] is released after cleavage by a myocardium-specific type II transmembrane protease—Corin that is thought to be also involved in BNP processing [14]. BNP is synthesized as a preprohormone of 134 amino acid residues, which after processing by corin or the ubiquitous endoprotease furin [15] is stored along with ANP in the atrial-specific granules as a 32 amino acid biologically active peptide and an inactive 76 amino acid N-terminal fragment [16,17]. Both the expression of corin and furin are upregulated in hypertrophy; however, the biological and clinical implications of this are still unclear [15,18]. Several different forms of proBNP, BNP, and NT-proBNP with varying molecular weights have been described in plasma, and are the result of posttranslational glycosylation and processing. Glycosylation of the N-terminal of ProBNP has recently been shown to suppress its processing by the endoproteases [19], and there is evidence of functional heterogeneity among the different forms [20,21]. Since most commercial assays for BNP and NT-proBNP are not specific to one form, these findings may explain the state of resistance to high endogenous BNP levels that occur in patients with severe heart failure, in which nonactive forms may be predominant [22]. When the myocardium is subjected to stress such as in heart failure, cardiac hypertrophy, or myocardial infarction, the ventricles become the main production site of ANP and BNP [2,23,24]. CNP on the other hand is mostly found in the brain, in chondrocytes, and in vascular endothelium [4,25]. Its expression has been recently documented in the myocardium and cardiac fibroblasts [5,26–28]. ProCNP, a peptide of 103 residues, is thought to be cleaved into the mature 53 residues form by furin [29]. Another 22 amino acid form of CNP is known to circulate in plasma [30]. All three mammalian cardiac natriuretic peptides ANP, BNP, and CNP share a conserved disulfide-linked ring of 17 amino acids required for biological activity (Figure 1).

The gene coding for ANP (Nppa) is well conserved across mammalian species [31,32] and is located along with the Nppb gene coding for BNP on human chromosome 1p36.2 and on the syntenic region of mouse chromosome 4 [33]. The gene coding for CNP (Nppc) maps to chromosome 2q24 in humans and chromosome 1 in mice [34]. Transgenic mice studies in which these genes have been respectively inactivated have yielded invaluable information on the physiologic role of these peptides: Mice without ANP developed non-salt-sensitive hypertension [35], while those lacking BNP yielded normotensive animals, which developed pressure-sensitive ventricular fibrosis [36]. Mice lacking CNP exhibited severe dwarfism and early death due in part to impaired endochondral ossification [37].

Natriuretic peptides act on target organs via membrane-bound receptors: NPR-A (or GC-A) [38], a transmembrane guanylyl cyclase-coupled receptor expressed in kidney, smooth muscle, vasculature, adrenal gland, brain, heart, testis, eye, intestine, and olfactory mucosa. It mediates most if not all the physiologic functions of ANP and BNP by generating the intracellular secondary messenger cGMP [39,40], which acts on several downstream targets: cGMP-dependent protein kinases (PKG), cGMP-gated ion channels, and cGMP-regulated phosphodiesterases (PDE) [41] (Figure 2). Mice lacking NPR-A exhibited cardiac hypertrophy, high blood pressure, and ventricular fibrosis [42,43]. Patients with mutations that lead to a decreased expression of NPR-A suffer from hypertension [44]. NPR-B (or GC-B) [45], the main receptor for CNP, is also coupled to guanylyl cyclase and is predominantly expressed in the brain [46]. It is also found in lung, adrenal, kidney, uterus, and ovarian tissue [47,48]. Mice with homozygous deletion of NPR-B have a phenotype similar to that of mice lacking CNP: dwarfism and female sterility [49]. In humans, patients with a rare form of short limbed dwarfism—acromesomelic dysplasia-type Maroteaux have a loss of function mutation in the NPR-B gene [50]. NPR-C [51], also known as the clearance receptor [52], was initially thought to be devoid of enzymatic activity, its putative function being to remove natriuretic peptides from the circulation by receptor-mediated endocytosis [53]. However, several studies reported coupling of NPR-C to inhibition of adenylyl cyclase [54] and stimulation of phospholipase C [55,56]. NPR-C was recently found to mediate the peripheral response of ANP and CNP in stimulating pancreatic secretions in the gastrointestinal system [57,58]. NPR-C represents 95% of all natriuretic peptide receptors and is expressed in several tissues; kidneys, adrenals, lungs, vascular wall, intestine, brain, and in all chambers of the heart [51]. Loss of function mutations of NPR-C in mice interfered with the ability to clear ANP and concentrate urine; they also caused skeletal deformities [52]. However,

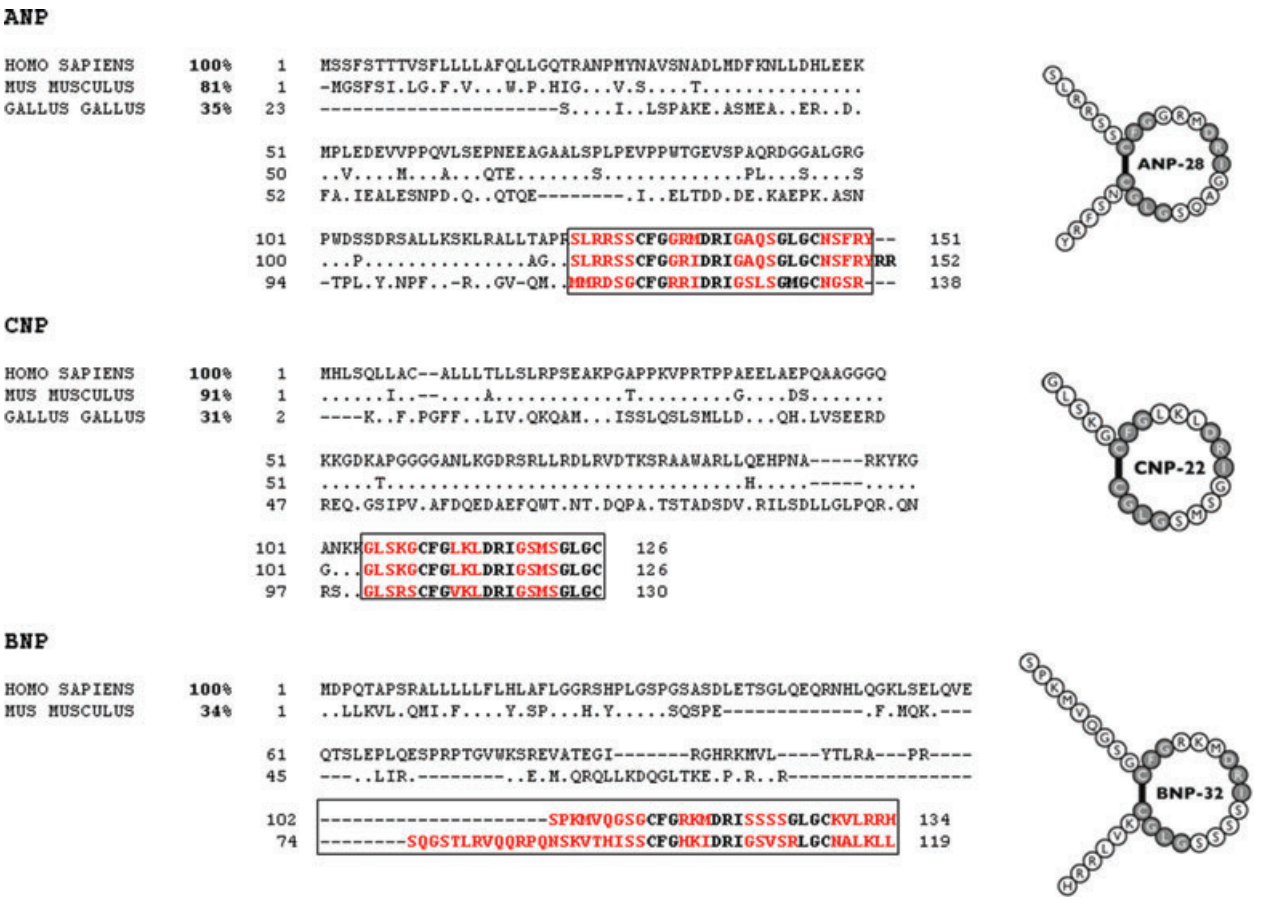

Figure 1 Sequence homology or pre-proANP, CNP and BNP. Depicted on the right are the active hormones (sequence also boxed). Note the highly conserved nature of ANP and CNP. All three hormones contain the conserved sequence CFGXXXDRIXXXXGLGC with the flanking cysteines forming a disulfide-linked ring required for biological activity.

the physiologic significance of this pathway is still uncertain.

The clearance of natriuretic peptides from plasma and tissues relies on two concurrent mechanisms: NPR-C-mediated internalization in clathrin-coated pits, [53] and proteolysis by nephrilysin, a ubiquitously expressed neutral endopeptidase (NEP 24.11) [59]. In pathological states such as during heart failure when levels of ANP and BNP are high, the proteolytic pathway contributes increasingly to the degradation of natriuretic peptides as NPR-C levels decrease and receptors become saturated [60]. The half-life of ANP ranges between 2 and 3 min while that of BNP averages 12 min in congestive heart failure. The longer half-life of BNP in plasma may be accounted for by the higher affinity of ANP to NPR-C, as well as the relative resistance to hydrolysis of BNP [61] and explains why measurements of plasma BNP levels were found to be more reliable than ANP levels.

Physiologic Function

The term "natriuretic" peptide was initially coined when de Bold et al. demonstrated that atrial extracts injected into rats led to profuse diuresis. It is now evident that natriuretic peptides have a wide range of biologic actions that target different organs and systems such as cardiovascular, neurological, digestive, respiratory, and immune. ANP and BNP have overlapping biologic effects; however, the phenotype of the knockout mouse models clearly indicates distinct physiologic functions for these peptides. ANP is mainly released as a response to increased intravascular volume leading to atrial myocardial wall stretch [62]. Its net effect is the reduction of cardiac preload and afterload in response to stress as well as modulating cardiac growth. At the level of the vasculature, ANP regulates basal blood pressure by increasing microvascular permeability [63]. It also induces the

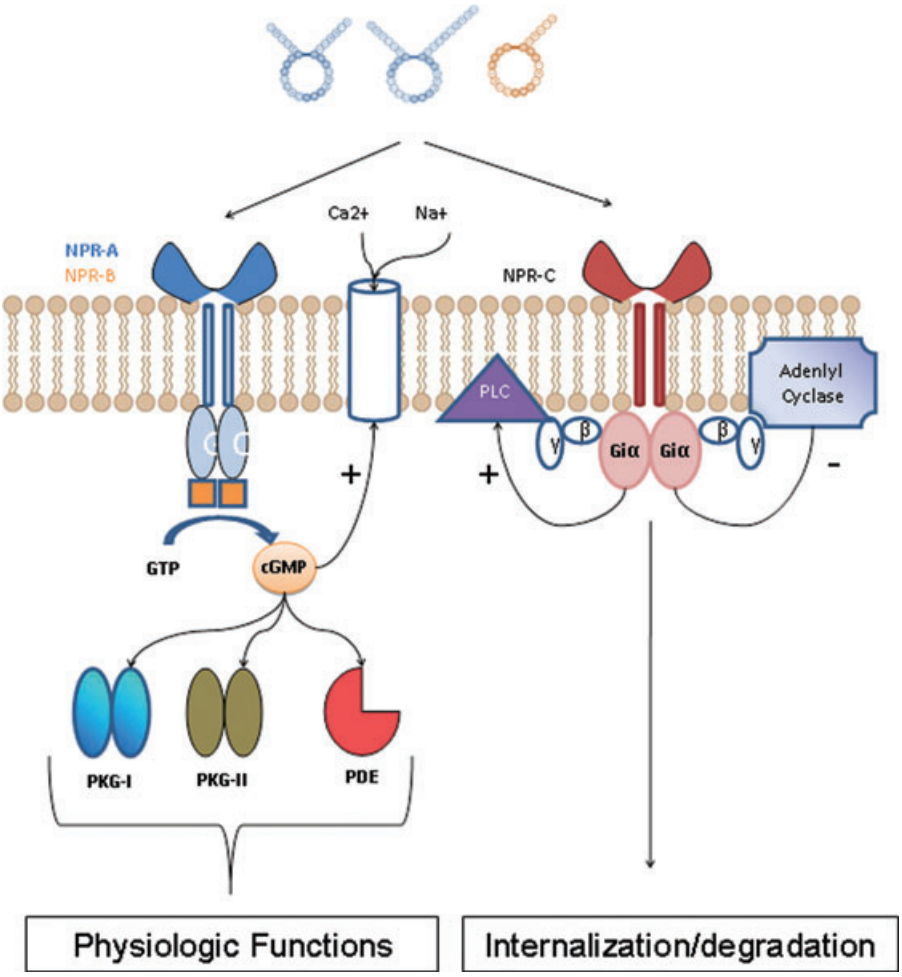

Figure 2 Mechanism of action of natriuretic peptides. NPR-A is the receptor that mediates the physiologic action of ANP and BNP by generating the intracellular secondary messenger cGMP, which acts on several downstream targets: cGMP-dependent protein kinases (PKG), cGMP-gated ion channels, and cGMP-regulated phosphodiesterases (PDE). NPR-C inhibits adenylyl cyclase and removes NPs from circulation via endocytosis in clathrin-coated pits. The affinity of the natriuretic peptides to their receptors is as follows: NPR-A = ANP > BNP >> CNP; NPR-B = CNP >> ANP > BNP; NPR-C = ANP > CNP = BNP.

relaxation of vascular smooth muscle cells, in response to acute increases in blood pressure [64], in a PKG-I-dependent mechanism the downstream effects of which lead to a reduction in cytosolic calcium as well as membrane hyperpolarization [65].

ANP acts directly on the kidney by dilating the afferent arteriole and constricting the efferent arteriole [66,67]. Angiotensin II-stimulated sodium and water transport in the proximal tubules is inhibited [68], while in the collecting ducts sodium absorption is reduced by the inhibition of amiloride-sensitive cation channel [69]. The net effect is a rise in glomerular filtration rate, and a decrease in sodium and water reabsorption. Blood pressure regulation also occurs through ANP action on the renin–angiotensin–aldosterone system (RAAS). It inhibits renin secretion through a PKG-II-dependent mechanism [70], and reduces aldosterone production at the adrenal gland level via PDE2 and by preventing the synthesis of steroidogenic acute regulatory protein (StAR) in the adrenal glomerulosa [71,72]. The cardiovascular modulating activity of ANP extends to the nervous system, where it suppresses salt appetite [73] and vasopressin (ADH) secretion from the hypothalamus [74], in addition to dampening sympathetic outflow [75].

Maintaining cardiorenal homeostasis by regulating fluid volume is but one aspect of the cardioprotective properties of natriuretic peptides. Evidence from transgenic mice suggests the ANP/BNP/NPR-A system in the

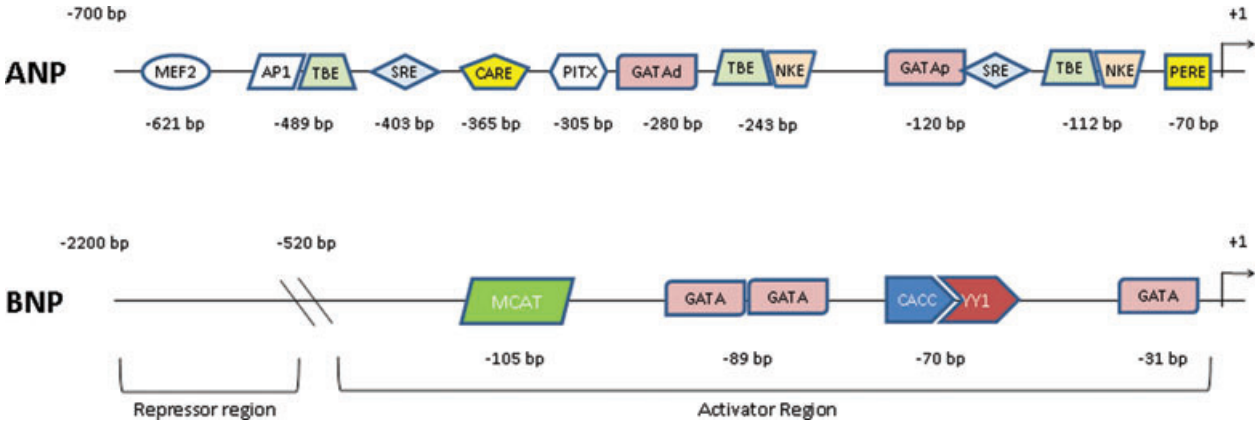

Figure 3 Schematic representation of the Rattus norvegicus ANP and BNP promoters showing the various regulatory elements identified so far. Transcription factors binding these elements have been identified. Many are essential for cardiac development or involved in growth or hormone regulation.

myocardium inhibits pressure-induced cardiac remodeling and hypertrophy [76–79]. BNP specifically acts by inhibiting ventricular fibrosis [36,80]. Although the mechanism is not fully understood, it may involve the induction of matrix metalloproteinases [81], and the inhibition of TGF-β [82,83]. Recent evidence reveals an antifibrotic action of ANP via inhibition of TGF-β1-induced Smad signaling [84]. However, whether ANP protects against ischemia-reperfusion injury is still controversial.

CNP's role in the myocardium has only begun to be elucidated as evidence shows it participates in blood flow regulation and prevents postmyocardial infarct reperfusion injury [6], perhaps by inhibiting platelet–leukocyte interaction [7] leading to a reduced inflammatory response in the injured myocardial wall. CNP's main function is at the level of blood vessels where it acts as a vasodilator in response to injury and suppresses reactive smooth muscle cell proliferation and intimal growth [85,86], including pulmonary vessels in which CNP was shown to alleviate induced pulmonary hypertension and fibrosis [87,88].

Other targets of natriuretic peptides include adipocytes in which ANP was shown to stimulate lipolysis [89]. This PKGI-mediated pathway [90] may partially explain cardiac cachexia occurring in heart failure during which ANP levels are elevated. The brain, which extensively expresses natriuretic peptides, NPR-B, and NPR-C receptors, has been the subject of several studies exploring the modulatory activities of these peptides in synaptic transmission, neurotransmitter release, and neuroprotection [91]. However, the physiologic and clinical significance of the actions of these peptides in the central nervous system remains to be elucidated.

Transcriptional Regulation and Impact on Congenital Heart Disease

The expression of natriuretic peptides is spatially—that is tissue specific, and developmentally regulated. ANP and BNP levels rise continuously during the embryonic phase of life in both atria and ventricles as cells differentiate into cardiomyocytes, only to stabilize postnatally in the atria while dropping precipitously in the ventricles [92]. In response to prolonged cardiac stress as in hypertrophy, hypoxia, and ischemia, the expression profile of the myocardium partly reverts to a fetal-like pattern [8] possibly as an adaptive response [93]. Fetal isoforms of metabolic enzymes, natriuretic peptides, and structural components of the cardiomyocyte such as α-skeletal actin, β-myosin heavy chain, and others are reinduced, increasing cardiac efficiency through a cocktail of biological actions leading to remodeling, decreased preload and afterload. As a highly conserved marker of this fetal gene program, analysis of the ANP promoter has brought insight and understanding of the transcriptional control mechanisms underlying these changes, as well as those governing cardiac growth and differentiation (Figure 3, Table 1).

Transcription factors that tightly regulate ANP have been found to be essential to the process of cardiac development (Table 1). Of those three have been associated with congenital heart disease in human: GATA4, Nkx2.5, and Tbx5 (Figure 4).

GATA4

The cardiac GATA family of transcription factors, specifically GATA4 has emerged as "master" regulator, on which inhibitory and stimulatory signals converge and

Table 1 Regulators of natriuretic peptides in heart development

TF	Role in heart development	Human heart defect
GATA-4	Growth and differentiation of myocardial and endocardial lineages	ASD, VSD, AVSD, DORV, dextrocardia, pulmonary stenosis
GATA-6	Outflow tract formation and proliferation of vascular smooth muscle cells	ND
Nkx2.5	Septation, conduction system development, and chamber specification	ASD, VSD, TOF, DORV, aortic stenosis, Ebstein anomaly, AV block
MEF2	Heart morphogenesis and terminal differentiation of cardiac myocytes	Coronary artery disease and sudden death
Tbx2	AV canal formation	Ulnar mammary syndrome
Tbx3	Outflow tract	Ulnar mammary syndrome
Tbx5	Atrial myocyte specification, conduction system development, and septum formation	Holt-Oram syndrome—isolated ASDs
Tbx20	Proliferation of endocardial and myocardial cells	Septal and valvular defects, cardiomyopathy
dHand	Chamber specification—right ventride	ND
FOG-2	Outflow tract development	Tetralogy of Fallot
Smad6	Endocardial cell differentiation	ND
Pitx2	Left–right axis formation	ND
Irx4	Ventricular specification	ND

ND = Not determined.

with which other transcription factors cooperate to induce ANP and BNP expression. GATA4 is essential for myocyte survival and differentiation [94] and for normal heart development; mice lacking GATA4 die *in utero* due to disruption of the ventral folding of the heart [95–97]. Patients with heterozygous GATA4 mutations exhibit a wide range of cardiac defects including atrial septal defects (ASD), ventricular septal defects (VSD), atrioventricular septal defects (AVSD), double outlet right ventricle (DORV), dextrocardia, and pulmonary stenosis [98]. These zinc finger proteins bind to the consensus sequence (A/T)GATA(A/G) [99]. As shown in Figure 3, two GATA-binding sites have been identified on the rat ANP promoter, located at −280 and −120 and three on the BNP promoter; one at −30 and the other two at −90 [100]. Through these motifs GATA-4 and GATA-6 stimulate the transcription of ANP and BNP, while mutational modification of these sites reduces significantly promoter activity [100–102]. Transcriptional activation of the ANP and BNP promoter in the ventricle in response to hormones such as angiotensin II or endothelin [103–105], or myocardial stretch [102,106] and to the β-adrenergic agonist isoproterenol [105] is mediated by GATA4. Importantly, knock-down of GATA4 in cardiomyocytes inhibits their hypertrophic response to α1-adrenergic agonists and endothelin [107]. Mice lacking one copy of the GATA4 gene have enhanced susceptibility to drug-induced cardiotoxicity [108] and impaired response to pressure overload [109] leading to heart failure. Thus GATA4 is essential for normal heart development and its impaired activity causes congenital heart disease. Since GATA4 is required for proper function of the adult heart, development of small molecules that enhance its expression or activity may hold promise as new therapies against heart failure.

Nkx2.5

Nkx2.5, an NK2 class homeodomain transcription factor, is another essential actor in cardiac development; transgenic mice lacking Nkx2.5 do not survive past ED10.5 due to a disruption in cardiac looping [110]. In human, mutations in Nkx2.5 were first found in association with atrial septal defects (ASDs) and conduction disturbances [111]. Today, mutations in Nkx2.5 account for 4% of congenital heart defects—most commonly ASD and conduction defects. Other defects observed include VSD, Tetralogy of Fallot (TOF), DORV, subvalvular aortic stenosis, and Ebstein anomaly [98]. Nkx2.5 binds target promoters through a specific and highly conserved DNA sequence termed NKE (for Nkx2.5 Response Element). ANP was the first gene identified as a target for Nkx2.5 [112]. The ANP promoter contains 2 highly conserved NKE sites located at -243 and -112 (Figure 3), which are required for atrial-specific expression of ANP [112,113]. Nkx2.5 acts as a collaborator of GATA4 and interacts physically with it to synergistically activate transcription of ANP and other cardiac genes [114–116]. Nkx2.5 also interacts with Tbx5 to form a stable ternary complex over composite NKE-TBE elements on target genes, such as ANP (Figure 3) and connexin-40 [117].

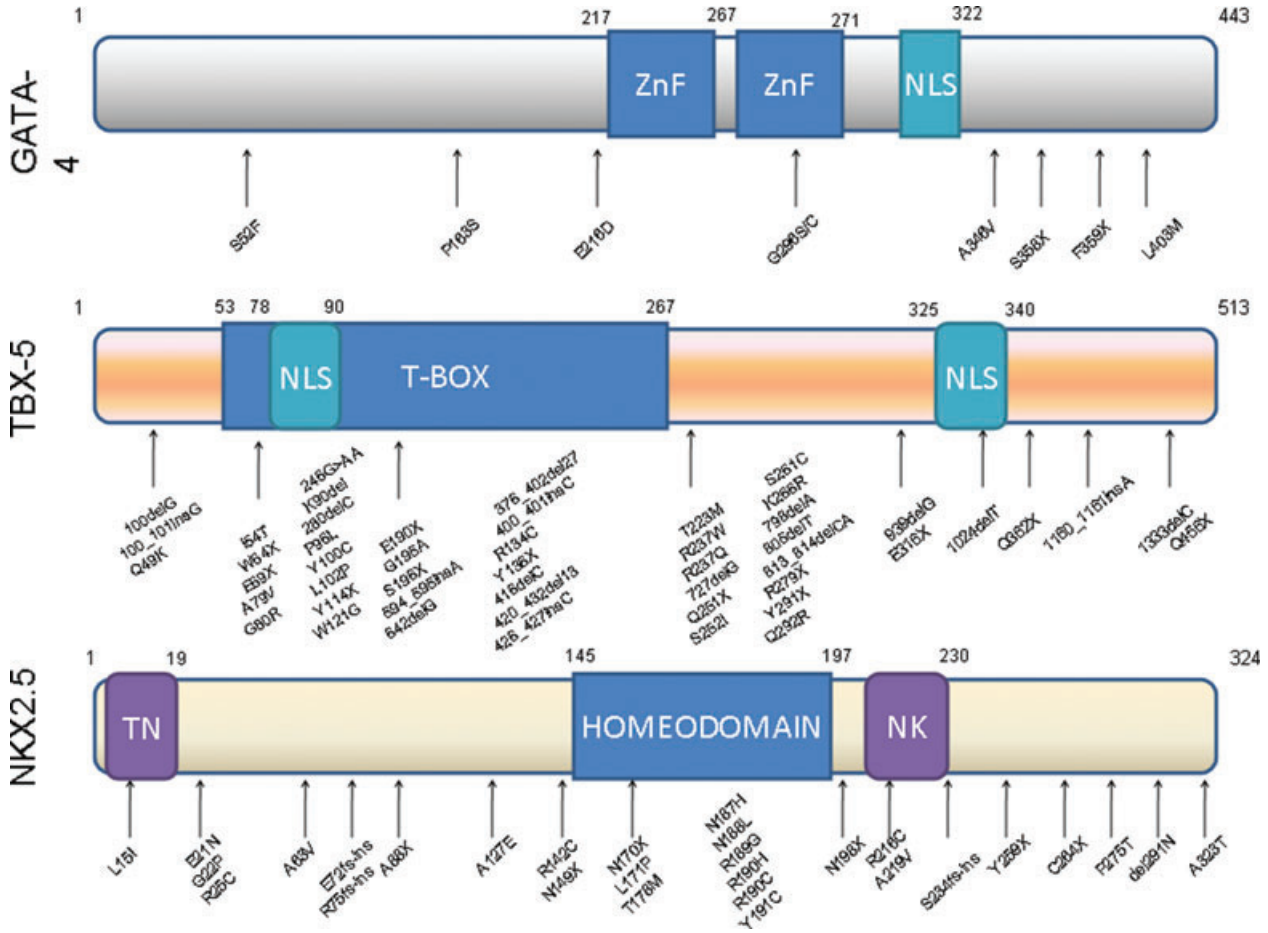

Figure 4 Schematics of the structure of transcription factor GATA4, Tbx5, and Nkx2.5. Important functional domains are depicted. NLS = Nuclear localization sequence; ZnF, Tbox, and Homeodomain are DNA-binding regions. A nonexhaustive list and location of disease-causing human mutations is depicted.

Tbx5

The T-Box family of transcription factors plays a prominent role alongside GATA4 and Nkx2.5 in cardiac development, specifically in atrial differentiation, septum formation, and development of the conduction system. Indeed, knocking out Tbx5 in mice is embryolethal due to abnormal heart tube morphogenesis and absence of atrial development [117]. Human genetic studies identified Tbx5 as the gene mutated in Holt–Oram syndrome, an autosomal dominant disease characterized by upper limb malformations, various cardiac septal defects and conduction abnormalities [118]. Tbx5 heterozygous animals exhibit a phenotype similar to the Holt–Oram syndrome [117]. Tbx5 is expressed predominantly in the heart, upper limb, and retina and its expression is closely linked to that of ANP during development: mice lacking Tbx5 did not express ANP [117]. Other members of the Tbx family Tbx2 and Tbx3—mutations of which cause ulnar–mammary syndrome [119], suppress the ANP promoter and inhibit the synergistic effects of GATA4, Nkx2.5, and Tbx5 in the primary myocardium and atrioventricular canal [120,121].

Other transcription factors have been described as regulators of the natriuretic peptide promoters: Serum response factor (Srf), Myocyte enhancer factor 2 (Mef2c) of the MADS box transcription factor family, Baf60c, Hand, Zfp260, and Pitx2 contribute to the transcription of ANP either by directly binding cis-elements or through recruitment to the promoter via GATA4 or Nkx2.5 [122–125]. Friend of GATA (FOG-2) [126], Jumonji [127] and Hey [128] inhibit GATA4 transactivation of ANP. Irx4, a member of the Iroquoix homeobox family of transcription factors is thought to be involved in the postnatal downregulation of ANP and mice lacking Irx4 continue to express ANP in the ventricle postnatally [129]. In the case

of BNP, the proximal promoter, which is sufficient for high level expression in the heart [102], contains binding sites for the YY1 [130] and KLF13 [131]. In xenopus, knockdown of KLF13 causes ASDs and hypotrabeculation [131]. KLF13 was found to cooperate with GATA4 raising the possibility that it may act as a genetic modifier of GATA4 in congenital heart disease.

Thus, transcriptional analysis of cardiac natriuretic peptide genes identified disease causing genes in human and furthered our molecular understanding of congenital heart disease (CHD). In particular, combinatorial interactions of transcription factors help explain how mutations in different genes lead to similar cardiac defects. This basic knowledge is being used in human genetic studies for the stratification of patients and will have impact on the management and care of asymptomatic of individuals with a family history of CHD.

In the coming years it will be interesting to determine whether mutations in the other regulators of ANP and BNP are also associated with human CHD, which has an incidence of 1–3% in the general population and accounts for 25% of human birth defects.

Clinical Applications

The considerable and consistent increase in plasma levels of ANP and BNP in hypertrophy and heart failure has earned these peptides a major role in the diagnosis and management of patients with congestive heart failure. ANP levels in healthy individuals averages 10 fmol/mL and rises 10–30-fold in left ventricular dysfunction [132], while BNP levels increases 300-fold from a baseline 1 fmol/mL [133]. This wide range of concentrations as well as the relative stability of BNP makes it an ideal diagnostic marker [134]. The landmark Breathing Not Properly Study showed that in the emergency care setting, measurement of BNP has proven to be an invaluable tool in confirming or ruling out the diagnosis of heart failure in patients with dyspnea. Patients with BNP levels <100 pg/mL are unlikely to have a failing heart as the etiology of their clinical presentation. While a level of >400 pg/mL is highly suggestive of the diagnosis, the gray zone 100–400 pg/mL requires further confirmatory tests, [135] as moderate increases can be attributed to other causes such as myocardial ischemia, renal dysfunction, and pulmonary diseases. BNP measurements allow risk stratification of patients as increasing levels are associated with severe heart failure and poor prognosis and are also used as surrogate markers to titrate and monitor treatment in the inpatient and outpatient setting [136,137]. Recently, BNP was suggested as an independent prognostic marker in the evaluation of asymptomatic patients with severe mitral regurgitation. Plasma BNP levels ≥ 105 pg/mL identified a subgroup of patients at a higher risk of left ventricular dysfunction or death, with an event-free survival rate of $29 \pm 8\%$ at 48 months postsurgery [138]. Natriuretic peptides assays, having a high negative predictive value, are being evaluated for use as screening tools for subclinical disease, as evidence has shown that pharmacologic therapy has significantly improved outcomes in patients with asymptomatic left ventricular dysfunction (ALVD) [139]. Indeed, the prevalence of ALVD in hypertensive and diabetic patients was found to be 5.1% and using NT-ProBNP assays by outpatient practitioners can rule out ALVD [140]. However, further studies in the form of randomized controlled trials are needed to establish which population profile to screen and to determine if screening would alter the natural history of left ventricular dysfunction [141].

Natriuretic peptides have been also considered as potential therapeutic agents for the treatment of various cardiac diseases. Synthetic ANP—Anaritide has been evaluated in patients with hypertension [142], heart failure [132,143,144], and contrast-induced nephropathy [145,146]. Contradicting results and no clear benefits have prevented Anaritide from joining mainstream therapies for these conditions. Recombinant BNP—Nesiritide has been approved for the treatment of acutely decompensated heart failure after randomized-controlled trials have shown that it improves hemodynamic function and general clinical status [9,147]. However, debates on its use are still ongoing as *post hoc* analysis has raised concerns of deleterious effects on renal function [148] and possible increase in a 30-day mortality [11]. Research continues to explore the possible therapeutic effects of natriuretic peptides: a recent pilot study has shown that it improves hemodynamics in children with dilated cardiomyopathy [149], and several studies have shown benefits of ANP and BNP in preventing cardiac remodeling in ischemic injury models of dogs [150] and in patients who have suffered from myocardial infarction [151–153]. The first human clinical trial of CD-NP, a chimeric peptide consisting of CNP and part of Dendroaspis NP given to healthy subjects, was shown to possess cyclic guanosine monophosphate-activating, natriuretic, and aldosterone-suppressing properties without inducing excessive hypotension [154], laying the ground work for further trials.

Conclusion

Research into natriuretic peptides has been a gateway to understanding the heart in development, health, and disease. Analysis of their promoters, expression, and

function has led scientists on the path of discovering molecular mechanisms of disease as well as the major genes involved in heart morphogenesis. Remarkably, the translation of these basic findings to clinical settings has occurred in record time producing new diagnostic and therapeutic tools. Their contribution to clinical practice is immense: physicians can reliably screen, risk-stratify, diagnose, and follow patients with congestive heart failure using a widely available and cost-effective assay used in all patient care settings [155]. Cardioprotective properties are being explored, with important implications for therapy and prognosis in patients suffering from heart disease. The cardiac involvement of CNP is gaining interest, and knowledge of the modulatory functions of natriuretic peptides in noncardiac systems such as the central nervous system and the gastrointestinal tract is expanding. New findings are likely to accentuate the importance of these peptides outside the cardiovascular system and may translate into further clinical applications.

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Conflict of Interest

The authors declare no conflict of interest.

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