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Review

Regulation of expression of atrial and brain natriuretic peptide, biomarkers for heart development and disease ☆

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ABSTRACT

The mammalian heart expresses two closely related natriuretic peptide (NP) hormones, atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP). The excretion of the NPs and the expression of their genes strongly respond to a variety of cardiovascular disorders. NPs act to increase natriuresis and decrease vascular resistance, thereby decreasing blood volume, systemic blood pressure and afterload. Plasma levels of BNP are used as diagnostic and prognostic markers for hypertrophy and heart failure (HF), and both ANF and BNP are widely used in biomedical research to assess the hypertrophic response in cell culture or the development of HF related diseases in animal models. Moreover, ANF and BNP are used as specific markers for the differentiating working myocardium in the developing heart, and the ANF promoter serves as platform to investigate gene regulatory networks during heart development and disease. However, despite decades of research, the mechanisms regulating the NP genes during development and disease are not well understood. Here we review current knowledge on the regulation of expression of the genes for ANF and BNP and their role as biomarkers, and give future directions to identify the in vivo regulatory mechanisms. This article is part of a Special Issue entitled: Heart failure pathogenesis and emerging diagnostic and therapeutic interventions.

1. Introduction

The heart of mammals expresses atrial natriuretic factor (ANF, ANP, a-type natriuretic peptide) and brain natriuretic peptide (BNP, b-type natriuretic peptide). Both proteins and their encoding genes have been identified decades ago [1–6], and their various physiological functions and expression in different organs have been studied extensively [7–11]. The overall effect of their function is to lower blood volume, reducing cardiac output and systemic blood pressure. In studies of vertebrate cardiogenesis, ANF and BNP have proven to be very useful and sensitive markers that discriminate chamber myocardium of the atria and the ventricles (positive) from primary, non-chamber myocardium such as the atrioventricular canal and pacemaker tissues (negative) [12]. Use of ANF regulation as a model system has led to the discovery of transcriptional mechanisms that control chamber and conduction system development [11,13].

Ventricular expression of the genes for ANF and BNP is down-regulated after birth (Fig. 1A–D). However, in the adult mammalian heart, their levels strongly increase during hypertrophy and HF (Fig. 1E, F). HF occurs when the heart is unable to provide sufficient pump action to distribute blood flow to meet the needs of the body, and is the end stage of a variety of cardiac diseases. HF is a common, disabling condition that can lead to death. Development of HF can result from hypertension causing increased ventricular wall stress and left ventricular hypertrophy, an important intermediate stage in transition to HF [14]. Other causes of HF include myocardial infarction (MI) and muscle loss, cardiomyopathy (the deterioration of muscle function), valve insufficiency and single-gene mutations [15–24]. Plasma levels of BNP and the N-terminal fragment of its prohormone, NT-proBNP, are used as diagnostic and prognostic markers for hypertrophy and HF [25]. Normal levels rule out acute HF in the emergency setting, whereas increased levels are associated with ventricular dysfunction. ANF is widely used in biomedical research to assess the hypertrophic response in cell culture or the development of HF-related diseases in animal models.

While a large body of knowledge is available on ANF and BNP function, and on conditions in which they are induced, little is known about the actual transcriptional mechanisms responsible for their regulation and induction in the heart. For example, the induction of ANF in the ventricle during hypertrophy is considered to be part of the induction of a fetal gene program [26]. This fetal program is a common feature of different pathological conditions including hypertrophy, ischemia, hypoxia, atrophy, where the heart experiences extensive remodeling and returns from utilization of fatty acids to carbohydrate for energy provision in increased hypoxic conditions. Other hallmarks are the induction of ANF and BNP, early response genes, such as *c-myc* and *c-fos*, and switches in isoform expression of genes for metabolic enzymes and sarcomeric proteins (e.g. induction of *Myh7* and *Acta1* in mouse). Triggered by increased mechanical

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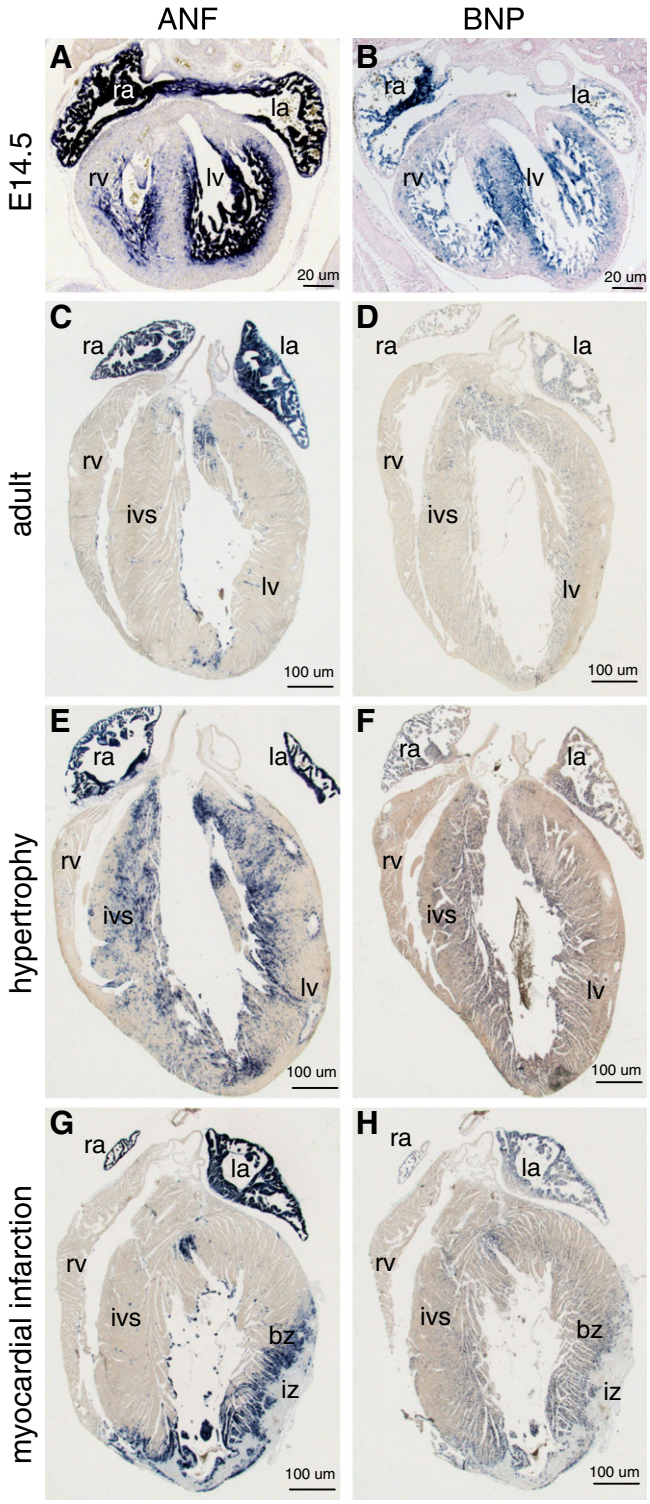

Fig. 1. Expression of ANF and BNP mRNA in sections of mouse embryonic, adult and diseased hearts. A, B. In E14.5 mouse embryos, ANF and BNP are expressed in both atrial and trabecular ventricular myocardium. The atrioventricular canal and outflow tract myocardium do not express ANF/BNP. C, D. Expression of ANF in the adult heart is restricted to the atria and the Purkinje fibers of ventricular myocardium, whereas BNP is expressed in atrial myocardium and in ventricular myocardium in a transmural gradient from the endocardial side. E, F. ANF and BNP mRNA are upregulated in the ventricles during hypertrophy. G, H. ANF and BNP are reactivated in the border zone after myocardial infarction. ra, right atria; la, left atria; rv, right ventricle; lv, left ventricle; ivs, interventricular septum; iz, infarct zone; bz, border zone.

load and hypoxic environment, all these changes until a certain point ensure cell survival under stress [27]. The regulatory DNA sequences of ANF controlling fetal ventricular expression on the one hand, and induction during disease on the other are different [28,29] and have not yet been identified. As a consequence, the transcriptional mechanisms remain to be elucidated. Insight into these mechanisms will help us to understand the pathology of hypertrophy and HF at the molecular level, and to understand the link between phenotype and ANF/BNP expression to use these molecules as biomarkers for cardiovascular disease more effectively. In this review we will discuss current insight into the expression patterns of ANF and BNP during development and cardiac disease, and the underlying mechanisms of gene regulation, focusing on the regulatory DNA sequences and interacting factors.

2. ANF and BNP expression profiles during development and disease

ANF was the first natriuretic peptide to be identified and purified from atrial extracts in 1981, when it was shown to increase natriuresis, diuresis and vasodilation [30]. But the spectrum of action was not limited to cardiovascular and renal systems. Receptors for ANF were identified in different organs including the kidney, lung, liver, adrenal cortex, and the small intestines, where it could regulate salt and water balance as well [31]. Moreover, ANF receptors [31] as well as bioactive peptide were also found in the brain [32–34]. Extensive work on the purification of a variety of active peptides in the 1980s revealed that in addition to ANF the brain contains another NP, therefore called BNP [2]. One of the actions of NPs in the brain is to inhibit release of adrenocorticotropic hormone, thereby decreasing aldosterone release and enhancing natriuresis. Furthermore, the ANF-ergic neurons inhibit arginine vasopressin release leading to diuresis [35]. Therefore, NPs expressed in the brain also serve to maintain optimal liquid homeostasis. Although isolated from the brain, BNP is predominantly expressed in the heart ventricles and mimics the pharmacological activity of ANF in regulation of blood pressure. Isolated ANF and BNP proteins were found to have a remarkably similar structure [2,30]. These NPs are encoded by *natriuretic peptide A* (*Nppa*) and *-B* (*Nppb*), respectively, which are positioned adjacent to each other and in close proximity (<15 kilo base pairs (kbp) distance) in the vertebrate genome [6,36,37]. Both genes are expressed in specific patterns in the developing and adult heart, and induced in particular cardiovascular pathological conditions.

2.1. Temporal expression patterns of NPs in the heart

Expression of ANF is initiated in the tubular murine heart (mouse embryonic day (E) 8) at the level of the future left ventricle. Thereafter, it is activated in the developing atria and the ventricles of the looping and ballooning heart [12,38]. When compact myocardium of the ventricles begins to form between E10-12, expression of ANF becomes restricted to the trabeculated layer, higher in the left ventricle than in the right. The expression of ANF is limited to differentiating chamber (future working) myocardium. The myocardium flanking the chambers, the sinus venosus, including the sinus node, the atrioventricular canal including the future atrioventricular node, and the outflow tract never express ANF [12]. Because of this property, ANF has been used extensively as a marker for differentiating chamber myocardium during cardiogenesis, which has led to the identification of transcriptional mechanisms for chamber and conduction system development [39]. In human fetuses, ANF mRNA is more abundant in the atria than in the ventricles [40], whereas in the ovine fetal heart atrial expression is lower than that of the ventricles during the last two-third of the gestation period [41].

In mammals during gestation and after birth, ventricular ANF expression decreases from 50% of atrial expression in human and 4% in mouse fetuses to about 1% in adult mammalian hearts [29,42,43].

Ventricular ANF expression becomes restricted to the subendocardial ventricular conduction system [44]. Progressive decline in ventricular ANF expression during development was reported in *Xenopus*, mouse and sheep [41,45]. However, in contrast to mammals, adult zebrafish and *Xenopus* frogs maintain ANF expression in their trabecular ventricles [46]. Taken together, the relative contribution of ventricular ANF is more pronounced in the embryo than in the adult heart.

The spatio-temporal expression profile of BNP mimics that of ANF [47]. BNP expression in the embryonic mouse heart exhibits a peak of expression at midgestation (E12.5) with the ventricles being the dominant source of expression [48]. Neither BNP mRNA nor BNP peptide was detected in human 12–17 week fetuses [49,50]. After birth BNP mRNA level increased in both mouse atrium and ventricle, but still did not reach the mid-gestation level [48]. In rat, bovine and human hearts ANF and BNP were restricted to the ventricular conduction system [51–53].

Four C-type natriuretic peptide (CNP) genes, CNP-1–4, were generated by chromosomal duplications. Of these, CNP-3 was tandemly duplicated to give rise to ANF and BNP before the divergence of tetrapods and teleosts. Later in evolution, specific lineages of CNP genes were lost in different vertebrate classes. For example, frogs have lost CNP-1 and CNP-2 [54]. Chicken (birds) has lost the ANF gene, but retained BNP and their predecessor CNP-3. Mammals have lost the CNP-3 gene, but retained CNP-4 as the only CNP gene. Although CNP was not detected in the mouse heart [55] or in the human fetal, normal adult and failing myocardium with Northern blot analysis [49], difference in plasma CNP level between aortic root and coronary sinus indicates its production in the human heart [56]. Moreover, CNP was detected in the rat and pig cardiomyocytes and endothelial cells within the heart [57].

2.2. Induction of NP levels and gene expression in response to heart disease

Upon cardiac cell stress, ANF and BNP are rapidly released from pre-stored granules. ANF and BNP are stored in the same secretory granules in the atria [58] and their concentration in the blood is expected to rise simultaneously and to the same extent. Indeed, studies show synchronous elevation of plasma ANF and BNP during the time-course of acute volume or pressure overload [59–61] as well as presence of both elevated ANF and BNP in chronic models of hypertension [62,63] (Fig. 2). However, in these studies, the rise of BNP in plasma in the period of 2–24 h after induction of volume overload is inferior compared to that of ANF [59,64]. More short-term experiments were performed with isolated atria or ventricles to estimate secretion of NPs in minutes after stimulation, which showed that both ANF and BNP were acutely secreted with a peak at about 20–30 min after atrial pacing [65,66] and already in 1–5 min after ventricular stimulation [67]. These results indicate the ability of both atrial and ventricular myocytes to rapidly respond to stress. The mechanisms of predominantly atrial secretion of ANF after mechanical or neurohumoral stimulation are discussed by Thibault et al. [68]. Long term experiments with chronic overload revealed some differences in atrial and ventricular secretion of the NPs. Secretion of ANF from the overloaded left ventricle of spontaneously hypertensive rats (SHR) was accompanied by the decrease in ventricular concentration of immunoreactive ANF, whereas atrial protein concentration was not changed compared to the control rats. In vitro studies with the isolated hearts showed that hypertensive ventricles contributed 28% of the total ANF released, while normotensive ventricles contributed only 8%. These experiments suggest that excess ANF is released from the

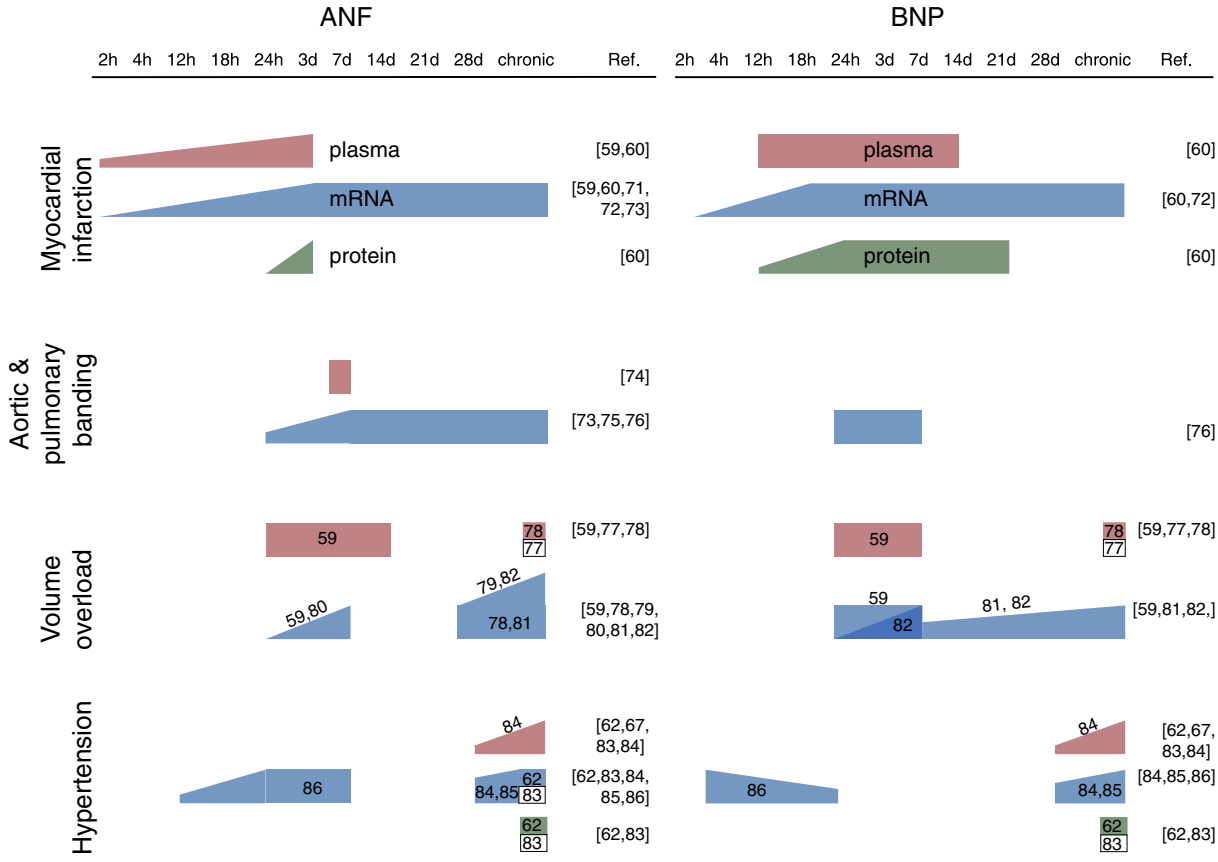

Fig. 2. Response of ANF and BNP in different animal models of cardiomyopathy [59,60,62,67,71–86]. Plasma levels of NPs are depicted in red, ventricular mRNA levels are depicted in blue and immunoreactive proteins in the ventricles are presented in green. The measured levels are plotted against the time after disease initiation.

ventricular stores [69]. However, in the settings of right ventricular hypertension, right atrial content as well as whole heart content of ANF was decreased [70], indicating atrial secretion of ANF. The difference can be explained by the differences in complex regulation of NPs release from the secretory granules and their de novo synthesis from an increased pool of mRNA.

In addition to the greater response of ANF to stress, its plasma level is also more sensitive to hemodynamic changes in the heart. Volume overload in dogs caused by furosemide showed rapid and gradual elevation of plasma ANF, which correlated with heart rate and left ventricular end-diastolic pressure (LVEDP), and was rapidly diminished 1 h after induced diuresis. In contrast, while elevated to a lesser extent, BNP could not diminish to the original level in 1 h after preload reduction [61]. Supporting this idea, the ACE inhibitor alacepril administered in patients with congestive heart failure was shown to decrease plasma ANF already 1 h after treatment, whereas it took more than 6 h for plasma BNP to decrease [87]. These findings are in agreement with the view that secretion and clearance of ANF and BNP are regulated differently [88]. The regulatory mechanism involves several neuro-humoral factors including renin–angiotensin system. In one of the hypertension models in rat, overexpression of the renin gene led to impaired induction of BNP release after volume or pressure overload [62]. Thus, plasma ANF level may be a more sensitive marker than BNP in fast response to hemodynamic changes in the blood.

Stress not only induces secretion of stored NPs, but also enhances their gene expression both in atrial and ventricular myocardium. Upregulation of ANF and BNP is initiated in the cardiomyocytes subjected to stress and, therefore, can be localized in the myocardium surrounding only right ventricular lumen after pulmonary trunk banding [89], only left ventricular lumen after aortic banding (Fig. 1E, F) or in the border zone after coronary artery ligation (Fig. 1G, H). Temporal regulation of ANF and BNP enhanced expression is also different in various conditions of cardiac disorders (Fig. 2). After myocardial infarction induced by isoproterenol injections in rats, BNF mRNA was upregulated in both ventricles at 18 h after injection, whereas ANF mRNA level gradually increased until significant levels 3 days after isoproterenol administration [59]. The same trend was observed in rats with aortocaval shunt, where both ANF and BNP plasma levels were steady elevated at 1 day and 7 days after surgery. Expression of BNF was induced only at 1 day after volume overload, but upregulation of ANF mRNA followed that of BNP only in 7 days after surgery [59,80]. Acute ventricular overload after MI [60,80], hypertension [86] and volume overload [80] leads to rapid and sometimes transient upregulation of BNP mRNA in the affected ventricular myocardium, whereas ANF upregulation follows BNP at later time points. These studies present BNP as a marker of acute myocardial stress on the gene expression level. However, measurements of ANF and BNP in some animal models of volume overload are contradictory—both ANF and BNP mRNA can be upregulated at the same time in the border zone of MI [90] or in the right ventricle of the hearts with pulmonary hypertension caused by aortocaval shunt before ventricular hypertrophy becomes evident [91]. BNP also showed increase in mRNA level during the transition from compensated to overt HF, since its expression was increased only during fibrosis development at the late stages of hypertrophy [85]. In patients with chronic volume overload caused by regurgitant heart valvular lesion, BNP mRNA was upregulated in the ventricles, whereas ANF mRNA level was similar to the control group [78]. Therefore BNP gene expression can serve as a marker of hypertrophy progression.

In the embryonic heart, NPs respond similar to pathological stimuli compared to the adult heart. Experiments with fetal rats, sheep and goats demonstrated that ANP plasma level was increased not only after stimulation with vasoconstrictors such as phenylephrine (PE), angiotensin II (AngII) and endotelin-1 (ET-1) [10], but also responded to systemic stress such as volume overload [92] and hypoxia [93,94]. Human fetuses increased their plasma concentration of ANF in anemic, acidemic, and hydropic conditions [95]. Both adult and embryonic mice deficient for the NPR-A receptor developed concentric hypertrophy, and fetuses produced more ANF and BNP mRNA already at E15.5 [96].

Taken together, completely different stimuli leading to cardiac hypertrophy, remodeling and HF are accompanied by increased ANF and BNP mRNA levels in the heart and protein levels in the heart and plasma. How such different pathophysiological stimuli cause similar induction of ANF and BNP expression, however, is not well understood.

2.3. ANF and BNP as markers of heart failure

For decades, plasma levels of the NPs have been used as a diagnostic marker in clinical settings to monitor the severity of hypertrophy and HF events [25]. ANF appeared to be less prognostic then BNP because of its shorter half-life in the blood [97,98]. Furthermore, levels of the amino-terminal fragment of the precursor peptide (NT-proBNP) were shown to be a more accurate marker in early diagnosis of HF [99] and more stable in frozen blood samples [100] compared to the mature carboxy-terminal BNP hormone. This makes NT-proBNP a widely used and reliable clinical marker. More recently, mid regional pro-ANP (MR-proANP) was evaluated for detection of cardiovascular diseases [101]. Together, both peptides are used as prognostic and diagnostic markers in many cardiovascular abnormalities such as hypertension, HF, left ventricular diastolic dysfunction, valvular stenosis and coronary artery disease [25]. BNP and NT-proBNP were elevated not only in the general symptomatic population, but also in patients with structural congenital heart defects such as systemic right ventricle, tetralogy of Fallot and univentricular heart, although the prognostic value of the markers in these cases has to be confirmed in a larger cohort [102]. Obesity is an independent risk factor for hypertension, left ventricular hypertrophy and HF. Studies linking obesity and hypertension suggest that activation of sympathetic and renin–angiotensin systems in obese individuals result in renal water and sodium retention, blood volume expansion and hypertension [103]. In parallel, lipid accumulation in the heart inhibits NPs mRNA and protein synthesis [104], the adipose tissue exhibits elevated expression of the clearance receptor NPR-C. Consequently, low level of ANF and BNP reduces NP-dependent lipolysis in adipocytes, therefore perpetuating obesity and sustaining decreased plasma level of NPs [105]. Although hypertension is marked by elevated levels of ANF and BNP, both healthy subjects and patients with cardiovascular diseases can have lower levels of measured NPs, which in this case predicts development of diabetes [103,106]. This paradox is a result of a complex physiological neuro-humoral response of the heart and was named ‘natriuretic handicap’ [105].

Although ANF and BNP are produced by the heart in response to a broad range of heart-related disorders, a differential diagnosis still requires assays in addition to NP level measurements. Combining myocytes injury marker cardiac troponin T and myocardial stretch marker NT-proBNP improves prognosis of mortality risk in patients with chronic HF [107]. Stressed myocardium is susceptible not only to mechanical stretch and injury, but also to inflammation and ventricular remodeling, and can be associated with renal dysfunction. Over the last decades, novel sets of biomarkers have emerged that represent specific molecular pathways and physiological processes [108,109]. Such multimarker approaches will help clinicians to phenotype and predict a particular disease, monitor and guide the treatment of HF patients.

3. Mechanisms of ANF and BNP gene regulation

Several signal transduction pathways have been identified that mediate the response of ANF and BNP to various stimuli. In the vast majority of cases, the proximal promoter sequences, just upstream of the transcription start site, were found to contain transcription factor binding elements or response elements that are involved in the

transcriptional response. In this section we summarize these pathways and elements, in the next section the in vivo relevance of these elements will be discussed.

3.1. Regulation of ANF and BNP expression by mechanical stress

Soon after the normal function of the heart changes due to hypertension, valve insufficiency or loss of myocardial muscle after infarction, cardiomyocytes experience additional load and stretch. Mechanisms of stretch-activated expression of ANF and BNP were studied in isolated cardiomyocytes, and atrial and ventricular preparation to separate the response of cardiomyocytes to strain from systemic response induced by neurohumoral factors. Mechanical stretch induces ANF, BNP and skeletal alpha-actin mRNA expression in neonatal ventricular cardiomyocytes [110] and atrial preparations [65,110,111]. The signal from mechanically-strained extracellular matrix propagates through the integrins and a cascade of intracellular kinases to activate p38 MAP kinase and NF-kappa-B [111–114] and promote binding of the latter to shear stress-responsive elements (SSREs) in the BNP promoter. In parallel with direct activation of BNP through p38 MAPK, mechanical strain stimulated synthesis of AngII and ET-1, which induced the ERK-signaling pathway acting on the BNP promoter [113,115]. Involvement of integrins and FAK (focal adhesion kinase) was also shown for activation of ANF expression both in vitro [116] and in vivo [117]. The sequences responsible for the stretch- and FAK-mediated activation are located within the 700 bp rANF promoter [118].

Two GATA binding sites at −84 and −95 bp as well as an NKE element at −387 bp in the rBNP promoter were found to mediate the stretch-induced response in ventricular myocytes and overloaded ventricles [110,119,120]. Mechanical strain activates ET-1 synthesis in cardiomyocytes [113], which in turn causes induction of ANF and BNP expression [111]. Increased GATA4 binding activity induced by pressure overload was inhibited by ET-1 receptor antagonist bosartan, suggesting an autocrine/paracrine regulatory mechanism after overload in ventricles [119].

3.2. Regulation of ANF and BNP expression through growth factors

Transforming growth factor beta (TGFβ) regulates multiple cellular processes in both adult and embryonic organisms including heart development and hypertrophy. Ligand binding leads to phosphorylation of receptor-regulated SMAD proteins, their association with SMAD4 and translocation of this transcriptional complex to the nucleus. TGFβ stimulates ANF and BNP mRNA expression in neonatal cardiac myocytes [121] and in rat hearts after MI [122]. The signal is transferred to the transcriptional machinery by downstream targets of TGFβ, TAK1-MKK3/6-p38MAPK. Later it was shown that the BNP promoter is differentially regulated by p38 isoforms. While p38α acts through AP-1 sites at −373 bp in the rBNP promoter, p38β activates BNP expression through the −90/−81 bp GATA sites [123].

Fibroblast growth factor (FGF) and insulin-like growth factor (IGF-1) are known to be involved in the organization of cytoskeletal and contractile structures of cardiomyocytes [124]. IGF-1, a circulatory hormone produced mostly by the liver, promotes growth of many cell types. However, it was shown to inhibit cardiomyocyte elongation and cardiac hypertrophy, and control Ca^{2+} homeostasis [125,126]. In accordance with these functions during HF progression, IGF-1 was shown to downregulate ANF expression in rat ventricular cardiomyocytes both in culture [127] and in vivo [128], whereas FGF increased ANF mRNA levels [127]. However, contradictory studies demonstrated pro-hypertrophic effects of IGF-1. Similar to its function in skeletal muscle hypertrophy [129], IGF-1 promoted hypertrophy of adult rat ventricular myocytes and induced ANF mRNA expression through a calcineurin-dependent mechanism and activation of the transcription factor Mef2C [130,131].

3.3. Role of G protein-coupled receptors in NP gene regulation

Several neurohumoral factors are involved in the hypertrophy response of the heart, including activation of ANF and BNP expression and secretion. AngII, ET-1, norepinephrine and epinephrine function through G protein-coupled receptors AT1 and AT2, ET-A and α- and β-adrenergic receptors, respectively. AngII is the main effector of the renin–angiotensin system, and was found to be involved in hypertrophy remodeling through activation of AT1 receptors on cardiomyocytes, fibroblasts and smooth muscle cells within the heart, which triggers G protein-coupled and non-G protein-coupled signaling pathways including MAP kinases (ERK 1/2, JNK, p38MAPK), receptor tyrosine kinases (PDGF, EGFR, insulin receptor), non-receptor tyrosine kinases (Src, JAK/STAT, FAK) and reactive oxygen species [132–135]. Recently, the AT2 receptor has received more attention because of its protective role in regeneration and repair processes involving c-kit(+) progenitor cells after MI [136]. However, AT2 was not involved in hypertrophy-related upregulation of ANF, since its expression in $AT2^{-/-}$ mice after aortic banding was not different from that of wild-type mice [137]. Besides direct activation of ANF expression through the AT1 receptor, AngII stimulated production of TGFβ in cardiac myocytes and fibroblasts [138], thereby influencing the regulation of NPs through TGFβ-GATA4 pathway [139]. AngII also stimulated ET-1, another pro-hypertrophic agent in the heart [140].

Vasoconstricting peptide ET-1 is produced primarily by the endothelium, but also by cardiomyocytes. Mechanical stretch induces upregulation of the ET-A receptor and ET converting enzyme-1 in stretched atrial myocardium, which in turn leads to enhanced ET-1 signaling and activation of ANF and BNP expression through stimulation of Ca2+/calmodulin-dependent kinase II (CaMKII), extracellular signal-regulated kinase (ERK) and possible inhibition of transcriptional repressor REST activity at the NRSE sites [111,141,142]. Normally, REST in complex with HDACs maintains low level of acetylation at the NRSE regions within the promoter of BNP and the 3′-UTR of ANF. After ET-1 stimulation, the level of H3 and H4 histone acetylation increased within ANF and BNP promoters [142] and around NRSE in the 3′-UTR of ANF [143], thereby increasing the activity of ANF and BNP transcription. Moreover, ET-1 activates binding of Yin Yang 1 (YY1) at position −62 bp in the hBNP promoter [144] and enhances cooperation between GATA4 and SRF, which interact with the −137/109 bp region in the rANF promoter [145].

Catecholamine hormones epinephrine and norepinephrine produced by the adrenal medulla stimulate the sympathetic nervous system, resulting in increased heart rate, muscle contraction, cardiac output and blood pressure. Adrenergic agonists phenylephrine (PE) and isoproterenol (ISO) are widely used to study the activation of NP expression during hypertrophy through adrenergic receptors α and β (ARα and Arβ), respectively [146,147]. The diversity of G proteins coupled to AR, activation of second messengers (IP3, DAG and cAMP) and protein kinases (PKC, PKA, MAPK), desensitization of the receptors and the beneficial role of β-blockers in the treatment of HF has been reviewed by Barry et al. [148]. Further studies provided many details regarding canonical and noncanonical activation of ERK1/2 through Arβ [149] and negative regulation of Arα-mediated ANF upregulation by Arβ-mediated signaling [150] .

Together, these studies describe the broad range of G protein-coupled receptors and their effectors on ANF and BNP regulation, where some of the pathways and DNA binding elements may still be unknown.

3.4. Other regulators of NP expression

Elevated levels of Ca^{2+} and Ca^{2+}-dependent phosphatase calcineurin have been reported to play an important role in the development of hypertrophy and HF [151]. L-type Ca^{2+} channels [152] and transient receptor potential subfamily C proteins (TRPCs) were shown to be involved in

the elevation of cytoplasmic Ca^{2+}, increase of ANF and BNF gene expression and development of HF. Knockdown of TRPC1 with siRNA prevented PE-, ET-1- and AngII-dependent upregulation of ANF and BNP [153]. Ca^{2+} elevation can also be a secondary effect of rising intracellular Na^+ due to the upregulation of the Na^+/H^+ exchanger (NHE) during hypertrophy. Increased Na^+ induces the reverse mode of the Na^+/Ca^{2+} exchanger (NCX) and increases Ca^{2+}, which in turn induces hypertrophy [154].

Increased thyroid hormone level is an independent risk factor for development of hypertrophy and HF. Triiodothyronine (T3) mediates ANF mRNA expression through the Akt/GSK-3beta/mTOR signaling pathway, which was shown to be dependent on AT1 receptors [155], exhibiting a cross-talk between T3 and renin–angiotensin systems.

Heart function relies on the balanced status and cross-talk between hormones, growth factors, signaling peptides and ion homeostasis. For example, AngII can directly stimulate expression of ANF and BNP through the AT1 receptors, but is also involved in upregulation of ET-1, which in turn is able to drive the hypertrophic program through the ET-A receptors on cardiomyocytes. T3 signaling was shown to be dependent on the AT1 receptor-mediated hypertrophic pathway [155], but also independently can activate synthesis of TGFβ in cardiomyocytes and intensify the effect [156]. Mechanical strain acts dually as well—direct activation of mechano-sensitive integrins and upregulation of autocrine hormones AngII and ET-1 are involved in ANF and BNP production. Thus, any deviations from normal homeostasis can lead to initialization and further acceleration of the hypertrophic program and ANF/BNP production.

4. In vivo mechanisms of ANF and BNP gene regulation: identifying the regulatory DNA elements

From decades of investigation, the regulation of ANF and BNP through their promoter elements has yielded a wealth of information regarding gene regulation during heart development and disease. However, the in vivo importance of the NP promoter elements was not well understood. In vivo studies, and especially those using transgenic reporter animals, proved to be very revealing in the actual capacities and roles of the NP regulatory sequences, and have provided reliable information regarding the regulation of ANF and BNP in development and disease.

The proximal promoter fragments of ANF (0.5 to 3.4 kbp) derived from various species including human, mouse, rat and frog (*Xenopus*) drive expression in the developing and adult atria of transgenic mice (Fig. 3). Habets et al. showed that the proximal promoter drives correct developmental expression of ANF in the heart, including activation in atria and ventricles and repression in the atrioventricular canal. This repression was found to be mediated by a T-box factor binding site (element) and an NK2-homeobox element in vivo, recognized by Tbx2 and Nkx2-5, respectively [13]. Moreover, Tbx2 mutants had atrioventricular canal defects and ectopically expressed ANF in the atrioventricular canal [157,158], whereas Tbx5 mutants completely failed to form chambers and to activate ANF [11]. The ANF promoter has thus been exceptionally useful in identifying the mechanism underlying atrioventricular canal and chamber development, and indirectly the development of the conduction system [39]. However, ventricular expression from this promoter fragment varied strongly between different transgenic lines, and on average was very low. Moreover, the expression pattern was not completely recapitulated in transgenic mice—it was ectopically expressed in the left and right sinus horns [13,29], mediastinal myocardium and compact ventricular myocardium even in the context of transcriptionally accessible *Hprt* locus [29]. Moreover, perinatal downregulation of the reporter gene in the ventricles was non-specific or not triggered at all in various independent transgenic lines.

The upregulation of ANF and BNP ventricular expression after divergent stimuli is commonly referred to as the fetal program. But how similar is the regulation of ANF and BNP during development and disease? One of the first in vitro studies showed a positive response of both 638 bp and 3003 bp rANF 5′-promoter fragments after stimulation of cultured cardiomyocytes with PE [167]. Moreover, injection of promoter–reporter plasmids in the ventricles of failing dog hearts also showed a positive response of these fragments [162]. These experiments suggested that these fragments contain stress-response regulatory elements of ANF. Later studies, however, revealed that this capability is not maintained in vivo, implicating more distal elements in the induction of ventricular reactivation of the reporter after TAC [28] (Fig. 3).

In vivo studies of BNP stress-responsive regions revealed that −408/+100 bp hBNP and −534/+4 bp rBNP promoter fragments are able to increase luciferase reporter activity after acute MI and AngII infusion, respectively [139,160]. In both cases, the level of the reporter activation was consistent with upregulation of endogenous BNP. These studies addressed the stress-response region of BNP, but the developmental activity profile of the promoter fragments was not investigated, making it difficult to conclude that all necessary information for BNP regulation is present in the proximal promoter. The BNP promoter fragment coupled to additional regulatory sequences had very limited activity in vivo [159]. Consistently, we also found that mouse BNP promoter fragments in transgenic mice did not show any activity in the hearts of several independent transgenic mouse lines (unpublished observations). The data suggest that the BNP promoter contains only a fraction of the regulatory information of BNP, possibly including response to hypertrophy, and that additional distal regulatory DNA regions are required to regulate its complete spatio-temporal expression pattern.

Three natriuretic peptide genes have been identified in vertebrates that are derived from an ancestral CNP-3 gene by duplication [54]. Mammals maintained two of these genes, *Nppa* and *Nppb*, positioned at a distance of only a few kbp from each other in the genome. Upstream of the BNP gene a large non-coding region is present. The regulatory sequences of ANF and BNP could be present anywhere in this locus, at distances from a few to hundreds or even thousands of kbp. Moreover, considering the very similar expression patterns and hypertrophy responses of ANF and BNP, these genes may share the same regulatory sequences. Similar examples could be found in the regulation of expression of other clustered genes such as *iroquois* (*Irx*) genes and the myosin heavy chain (MHC) genes.

The *Irx* genes are found from nematodes to humans. Comparative studies propose independent duplication events in ancestors of the insect and vertebrate lineages, resulting in three-gene clusters. More recently, the whole ancestral three-gene cluster was duplicated in vertebrates giving rise to paralogous clusters *IrxA* and *IrxB*, located on different chromosomes. Both clusters display conserved orientation of the three transcripts and distribution of highly conserved non-coding regions, playing a role of cis-regulatory elements [168,169]. Physical interaction of the promoters of the first two genes in each cluster suggests co-regulation of these genes and explains their similar expression pattern, whereas the third genes in the clusters stand apart and usually have divergent expression patterns [170]. It has been discussed that the sharing of regulatory elements by the genes has kept them together in a cluster during long course of vertebrate evolution [168].

The two cardiac myosin heavy chain (MHC) genes, α- and β-MHC, form a cluster of adjacently positioned genes formed by a genome duplication event. The two genes are reciprocally regulated in the ventricle during development and in adult conditions such as hypothyroidism and pathological cardiac hypertrophy. The β-MHC is the major isoform expressed in the fetal ventricle, but is downregulated to very low levels around birth. In contrast, α-MHC is strongly induced around birth and becomes the major isoform in the mouse heart (note that in human β-MHC is the major isoform in the postnatal ventricle). During conditions of hypertrophy, hypothyroidism or aging, expression of the two isoforms is reversed, so that β-MHC is re-expressed in the cardiac myocytes while α-MHC is downregulated [171]. Their distinct spatio-temporal profiles

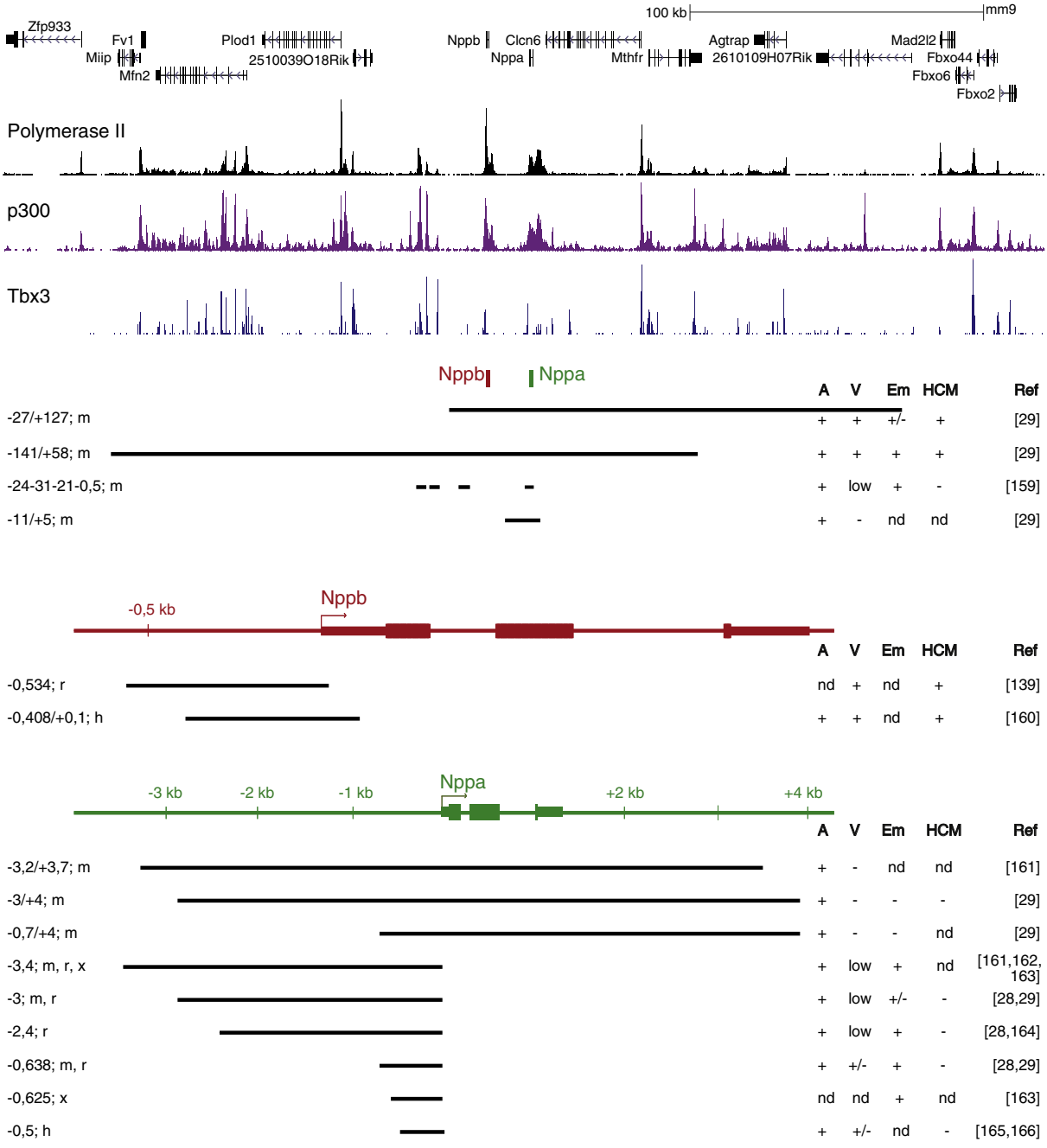

Fig. 3. Overview of the ANF-BNP genomic locus and the activity of regulatory sequences in vivo. Overlap of the gene positions with ChIP-seq data sets for Polymerase II, p300 [175] and Tbx3 [173] is shown in black, magenta and blue, respectively. The *Nppb* locus is depicted in red and the *Nppa* locus in green. Regulatory fragments studied in transgenic mice are depicted in black [28,139,159–166]. m, mouse; r, rat; h, human; x, xenopus; A, atria; V, ventricle, Em, embryonic heart; HCM, hypertrophic cardiomyopathy; +, expression; -, no expression; +/-, expression in some lines; nd, not determined.

are independently controlled by the promoters of the duplicated genes, but the isoform switch is coordinately regulated by thyroid hormone and response elements in the promoters. In addition, three miRNAs encoded by introns of the MHC genes, miR-208a, miR-208b and miR-499, regulate a set of transcription factors which modulate thyroid hormone signaling and govern the MHC switch [172]. Thus the α-MHC/β-MHC gene cluster contains information required for the coordinated regulation of these genes by shared pathways. The examples of the Irx clusters and the α-MHC/β-MHC locus suggest that the ANF/BNP gene locus also harbors cis-regulatory elements simultaneously regulating ANF and BNP, or that ANF and BNP are coordinatedly regulated by shared signaling mechanisms or non-coding RNAs.

The use of bacterial artificial chromosomes (BAC) allows the functional testing of over 200 kbp of genomic DNA. Studies with BAC transgenic mice showed that the regulation of ANF in the developing heart is controlled by distal regulatory elements in addition to the basic 0,7 kbp promoter. Fetal ventricular activity was found to require enhancer(s) between −141 and −27 kbp relative to the ANF gene, and the ventricular transmural pattern sequences within −27 to +58 kbp. Interestingly, the stress response region for the transgene was also found to require the −27 to +58 kbp region [29]. Three distal elements, −34 kb, −31 kb and −21 kb upstream ANF, were shown to be involved in ANF regulation. A construct in which all three fragments were fused provided correct ventricular activity

and transmural pattern of the transgene, potentially through the repression by the Hey2 transcriptional repressor in the compact myocardium. This −34-31-21-ANF-LacZ construct recapitulated embryonic and adult expression of ANF, which was dependent on Nkx2.5 expression, but, consistently with the findings of Horsthuis et al. [29] did not contain regulatory elements that respond to pressure overload and perinatal heart failure [159].

Regulatory elements of the ANF/BNP gene cluster can probably be identified by their co-occupancy by transcription factors and particular histone modifications in heart tissue [173,174]. Chromatin immunoprecipitation followed by massive parallel sequencing (ChIP-seq) allows mapping of the sites occupied by these factors across the whole genome. Promoter regions of ANF and BNP as well as more distal elements within the locus have been shown to be occupied by Gata4, Nkx2-5, Tbx3, enhancer-associated factors p300 and Polymerase II in vivo [173,175]. Moreover, ChIP-seq revealed the occupancy of the Nppa/Nppb by several transcription factors in HL-1 cells [174]. Transcriptional activator Tbx5 in cooperation with Nkx2.5 activates expression of ANF in the embryonic ventricles [11]. Tbx5 and Tbx3 belong to the same subfamily of the T-box transcription factors expressed in the heart and were shown to occupy the same binding sites [173]. Therefore, available Tbx3 ChIP-seq data can be used for analysis of ANF and BNP regulatory regions (Fig. 3).

Genome-wide association studies of genetic variants associated with levels of NT-proBNP identified variants in the *CLCN6* gene adjacent to ANF [176]. CLCN6 protein function could influence NT-proBNP levels. Alternatively, the *CLCN6* region may harbor regulatory sequences for BNP. We currently use a BAC transgenesis approach to identify the regulatory sequences, and preliminary data indicates that the region from −141 to +2 kbp relative to ANF gene contains all information required for correct spatio-temporal expression of BNP during heart development and its ventricular upregulation in TAC model of hypertrophy and after MI.

5. Conclusion and future directives

Analysis of ANF expression and regulation during development of the heart has provided important mechanistic insights into the development of the chamber myocardium and the conduction system of the heart. The ANF promoter has proven to be a useful tool for unraveling the mechanisms of transcriptional regulation in the heart, showing for example the importance of the T-box factors in heart patterning. Analysis of transcriptional regulation of ANF and BNP in different animal models of cardiomyopathy demonstrated the use of NPs in biomedical research to assess hypertrophic response in the development of HF, which is in agreement with their extensive application as biomarkers in a broad range of cardiovascular diseases in clinical practice. However, the regulation and regulatory sequences of ANF and BNP proved to be more complex than initially thought. Proximal regulatory sequences are not sufficient to control either correct spatio-temporal expression or stress-induced upregulation of these genes. Future research may focus on the identification and functional analysis of the regulatory sequences of ANF and BNP involved in these processes in vivo. Chromatin immunoprecipitation-sequencing and chromatin conformation capture technologies combined with reporter mice should allow the identification and functional assessment of these regulatory sequences in the near future. Thereafter, the composition of the transcriptional complexes acting through these sequences and the upstream signaling networks can be identified, which will provide the insights necessary to effectively use the NP genes as tools to study disease mechanisms and as predictable biomarkers.

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