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Emerging Roles of Natriuretic Peptides and their Receptors in Pathophysiology of Hypertension and Cardiovascular Regulation

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Abstract

Thus far, three related natriuretic peptides (NPs) and three distinct receptors have been identified, which have advanced our knowledge towards understanding the control of high blood pressure, hypertension, and cardiovascular disorders to a great extent. Biochemical and molecular studies have been advanced to examine receptor function and signaling mechanisms and the role of second messenger cGMP in pathophysiology of hypertension, renal hemodynamics, and cardiovascular functions. The development of gene-knockout and gene-duplication mouse models along with transgenic mice have provided a framework for understanding the importance of the antagonistic actions of natriuretic peptides receptor in cardiovascular events at the molecular level. Now, NPs are considered as circulating markers of congestive heart failure, however, their therapeutic potential for the treatment of cardiovascular diseases such as hypertension, renal insufficiency, cardiac hypertrophy, congestive heart failure, and stroke has just begun to unfold. Indeed, the alternative avenues of investigations in this important are need to be undertaken, as we are at the initial stage of the molecular therapeutic and pharmacogenomic implications.

Keywords

Natriuretic peptides; natriuretic peptide receptors; gene-targeting; cardiovascular events

Introduction

Almost 26 years ago, the pioneer discovery by de Bold et al. (1) demonstrated that atrial extracts contained natriuretic activity which led them to isolate “atrial natriuretic factor/peptide (ANF/ANP)” and to establish the field of natriuretic peptides (NPs). The NPs are a group of peptide hormones that play important roles in the control of renal, cardiovascular, endocrine, and skeletal homeostasis (2–5). ANP is the first described member in the NP hormone family that elicits natriuretic, diuretic, vasorelaxant, and antimitogenic effects, all of which are directed to the reduction of body fluid and blood pressure homeostasis (4). Later, two other members, B-type or brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), were identified (6,7). ANP and BNP are predominantly present in the heart and circulate in the plasma, whereas CNP is largely present in the vasculature. Three subtypes of natriuretic peptide receptors have been identified, namely NP receptor-A (NPRA), NP receptor-B (NPRB), and NP receptor-C (NPRC). Both NPRA and NPRB contain an extracellular ligand-binding domain, a single transmembrane spanning region, and an intracellular protein kinase-like homology domain (KHD) and guanylyl cyclase (GC) catalytic domain (8,9). Interestingly, both ANP and BNP

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activate NPRA, which produces second messenger cGMP in response to hormone binding; however, CNP activates NPRB, which also produces cGMP, but all three natriuretic peptides indiscriminately bind to NPRC, which lacks the KHD and GC catalytic domain (10). The discovery of structurally related NPs indicated that the physiological control of blood pressure and body fluid homeostasis is complex. This complexity is further enhanced by the prevalence of at least three sub-types of NP-specific receptors. A combination of biochemical, molecular and pharmacological aspects of NPs and their prototype receptors have revealed hallmark functions of physiological and pathophysiological importance including; renal, cardiovascular, neuronal, and immunological aspects in health and disease (5,11,12).

Background and Nomenclature of Natriuretic Peptides

ANP is primarily synthesized in the heart atrium, which elicits natriuretic, diuretic, vasorelaxant, and antimitogenic effects, all of which are largely directed to the reduction of blood volume and blood pressure (1,3,13). Both, BNP and CNP also exhibit biochemical and structural similarities to ANP but each of the three peptides is derived from a separate gene (14). Although, ANP, BNP, and CNP have homologous structure, bind to specific cell surface receptors, and elicit some discrete biological functions (3,15). BNP and CNP were initially isolated from the brain, however, BNP is predominantly present in the cardiac ventricle and CNP is primarily present in endothelial cells (14). All three NPs contain highly conserved residues with a 17-member disulfide ring but deviate from each other in flanking sequences. The primary structure deduced from cDNAs suggested that ANP is synthesized first as the 152-amino acid prepro-ANP molecule that contains sequences of active peptides in its carboxyl-terminal region, and major form of circulatory ANP is a 28-residue circulating hormone (16). Different lengths of sequences of ANP were synthesized for studies of structure-activity relationship, and it was indicated that the ring conformation of ANP molecule with a disulfide-bonded loop is essential for its activities (3).

The amino acid sequence of ANP is almost identical across the mammalian species, except for position 10 which is isoleucine in rat, mouse, and rabbit; however, in human, dog, and bovine, ANP has methionine in this position. BNP (17) and CNP (18) were both isolated from porcine brain extracts on the basis of their potent relaxant effects. Soon, it was established that BNP is predominantly synthesized and secreted from the heart (19). Similarly, CNP is predominantly localized in the central nervous system and endothelial cells and is considered a non-circulatory natriuretic peptide hormone (20). Like ANP, both BNP and CNP are synthesized from large precursor molecules and the mature bioactive peptides contain 17-residue loop bridged by an intramolecular disulfide bond. In essence, 11 of these amino acids are identical in biologically active ANP, BNP, and CNP; however, the amino- and carboxyl-terminus vary in length and composition (Fig.1). Among the species, ANP and BNP exhibit most variability in primary structure, but CNP is highly conserved across the species.

Synthesis and Secretion of Natriuretic Peptides

The three natriuretic peptides ANP, BNP, and CNP have highly homologous structure, but they have distinct sites of synthesis. Both ANP and BNP are predominantly synthesized in the heart, and ANP concentrations range from 50- to 100-fold higher than BNP. It is generally believed that following the processing of 151-amino acid preprohormone to 126-residue prohormone molecule, the cleavage and secretion of biologically active mature 28-residue ANP molecule occurs predominantly in response to atrial distension (4). However, the secretion of ANP from the heart is enhanced in response to a number of agents and settings such as angiotensin II, arginine-vasopressin, endothelin and head-down water immersion (21–25). BNP is also synthesized as a 134-amino acid preprohormone and is processed to yield a 108 residues prohormone molecule. The processing proBNP molecule yields 75-residue amino-terminal-BNP and a 32-residue biologically active circulating BNP molecule (17,26).

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The atrium is the primary site of synthesis for both hormones within the heart, however, ventricle also produces both ANP and BNP but at the level 100- to 1000-fold less than the atrium, respectively. Upon secretion, the cleavage of 126-amino acid ProANP molecule to generate nature 28-residue ANP is catalyzed by a serine protease, which is known as corin (27,28). It has been observed that the difference in the natriuretic peptide concentrations also correlate with mRNA levels (29). Interestingly, the expression of both ANP and BNP increases dramatically in both the atrium and ventricle in cardiac hypertrophy (30), nevertheless, the ventricle becomes the primary site of synthesis and release for BNP. It is believed that in ventricle, the BNP synthesis is regulated by volume overload, which activates ventricular wall stretch and the hormone synthesis is enhanced at the transcriptional level (31,32).

In essence, ANP and BNP show similar hemodynamic responses, however, BNP exerts a longer duration of action and causes enhanced rather than blunted natriuretic responses as compared with ANP (33,34). Cardiac atrium expresses almost 50- to 100- fold or even higher ANP mRNA levels as compared with extracardiac tissues (4,35). Interestingly, higher ventricular ANP is present in the developing embryo and fetus, nevertheless, both mRNA and peptide levels of ANP decline rapidly during the prenatal period (36). However, ANP gene expression in ventricle is reinducible postnatally in response to phenylephrine administration, after-load stress, and myocardium infarction (37). Indeed, the mRNA levels of BNP are markedly lower than ANP in heart, however, the BNP concentrations are higher in the ventricle as compared with both neonatal and adult rat hearts, but the reduction in the ventricular expression of BNP is far less than ANP in the adult hearts (38).

On the contrary, CNP does not seem to behave as a cardiac hormone and its levels are extremely low in the circulation (39). CNP is largely present in the central nervous system (40), vascular endothelial cells (41–44), and chondrocytes (45). CNP is believed to be synthesized as a 103-amino acid prohormone molecule and is thought to be cleaved as 53-residue peptide by an intracellular endopeptidease furin, which is believed to yield 22-amino acid biologically active CNP molecule (46). It has been suggested that the secretion of CNP is stimulated by various cytokines (41,42) and also by shear stress (47). D-type natriuretic peptide (DNP) represents an additional member in the natriuretic peptide hormone family (48,49). DNP is present in the venom of the green mamba (Dendroaspis angusticeps) as a 38-amino acid peptide molecule. In addition, a 32-amino acid peptide termed urodilatin (URO) is identical to C-terminal sequence of pro-ANP and appears to be present only in urine (50,51). It was initially purified from human urine and is presumed to be only synthesized in the kidney (52). URO is not present in the circulation and appears to be a unique intrarenal natriuretic peptide with unexplored physiological significance (52,53). The studies with immunohistological staining indicated that URO is largely present in the cortical tubules around the collecting ducts of the kidney (54–56).

Structure, Topology and Signaling of Natriuretic Peptide Receptors

Molecular cloning and expression of cDNA led to identify and characterize the primary structure of three distinct subtypes of natriuretic peptide receptors (NPRs), which are currently designated as natriuretic peptide receptor-A (NPRA) (9,57), natriuretic peptide receptor-B (NPRB) (8), and natriuretic peptide receptor-B (NPRC) (58). The three receptor subtypes (NPRA, NPRB, and NPRC) constitute natriuretic peptide receptor family; however, they differ in terms of their ligand specificity and transmembrane signal transduction activity (Table I). The general topological structure of NPRA and NPRB is consistent with at least four distinct domains (Fig. 2). As such, the entire coding region of both NPRA and NPRB is separated by a single transmembrane spanning region into extracellular ligand-binding domain and intracellular protein kinase-like homology domain, also referred to as kinase homology domain (KHD) and guanylyl cyclase (GC) catalytic domain (8,9). NPRA and NPRB are also referred

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to as GC-A and GC-B, respectively, (59). The transmembrane GC receptors contain a single cyclase catalytic active site per polypeptide molecule, however, based on the structure modeling data (60) two polypeptide chains seem to be required to activate the function of NPRA (61,62). The dimerization region of the receptor has been suggested to be located between the KHD and GC catalytic domain that have been predicted to form an amphipathic alpha helix structure (63,64). The NPRB has the overall domain structure similar to that NPRA with binding selectivity to CNP, also generates the second messenger cGMP (7,63,65,66). NPRA is the dominant form of the natriuretic peptide receptors found in peripheral organs and mediates most of the known actions of ANP and BNP (5). Whereas NPRB is localized mainly in the brain and vascular tissues, is thought to mediate the actions of CNP in the central nervous systems and also in vascular bed (7).

The third member of the natriuretic peptide receptor family, NPRC, constitutes a large extracellular domain of 496-amino acids, a single transmembrane domain, and a very short 37-amino acid cytoplasmic tail that bears no homology domain of any other known receptor proteins. The extracellular region of NPRC is approximately 30% identical to NPRA and NPRB. Ligand receptor binding studies have shown that NPRC has much less stringent specificity for structural variants of ANP than does NPRA or NPRB (67). The extracellular domain of NPRC possesses two pairs of cysteine residues along with one isolated cysteine near the transmembrane domain, three potential signals for N-glycosylation and several serines and threonines for O-linked glycosylation sites (58). Earlier, it was proposed by default that NPRC functions as a clearance receptor to clear natriuretic peptides from the circulation (68), however, several studies have also provided the evidence that NPRC plays roles in biological actions of natriuretic peptides (69,70).

All three natriuretic peptides (ANP, BNP, CNP) potently increase cGMP in target tissues in a dose-dependent manner (71–74). The production of cGMP is believed to result from ligand binding to the extracellular domain of NPRA or NPRB, which probably allosterically regulates an increased specific activity of the GC-coupled receptors (2,5,75–78). The juxtamembrane hinge structure of NPRA undergoes a significant conformational change in response to ligand binding, and it may play an important role in the transmembrane signaling process (64,79). The amino acid sequence near the transmembrane region is well conserved in NPRA and contains several closely located proline residues and a pair of cysteine residues. Mutation of one of the prolines does not affect ligand binding but blocks GC catalytic activity of NPRA (64). However, in the juxtamembrane hinge region, the elimination of the disulfide bond between cysteine residues results in constitutive receptor activation. These findings suggested that the juxtamembrane hinge region of NPRA may play a critical role in receptor activation and signal transduction mechanisms of GC-coupled receptors.

Previous findings have indicated that binding of ANP to the receptor by itself is probably not sufficient to stimulate GC catalytic activity and requires ATP (80–82). It was suggested that ATP acts directly by allosteric regulation of GC catalytic activity of NPRA. The ligand binding and the interaction of ATP with the KHD increase cGMP production without affecting affinity for the substrate (83–85). It has been suggested that GC catalytic domain cannot be activated by ANP alone without ATP-binding to KHD region of NPRA (80,86,87). Further studies provided the essential evidence that ATP binding to KHD of the receptor is important for receptor-effecter coupling of GC family of receptors (78,81,88,89). Deletion of the KHD of NPRA and NPRB receptors also suggested that KHD represses the GC catalytic activity of NPRA receptors (15,90). Both NPRA and NPRB contain a glycine-rich ATP binding motif within the KHD, which is known as glycine-rich cluster sequence (81,84,88,89).

The glycosylation sites from GC-coupled receptors are mapped onto the NPRA binding domain and have been found to be scattered on the surface of the receptor with the exception of the

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hormone binding site and dimer interface of the receptor (91). Previously, it has also been suggested that glycosylation is essential for the ligand binding activity of NPRA (92–94). The glycosylation sites in GC-coupled receptors have been implicated to be important for proper folding and stability of the receptor proteins (94–96). However, the exact role of glycosylation sites in the ligand binding of the receptor has not yet been provided. It should be noted that there is no appreciable conservation of the precise position of the glycosylation sites within the members of GC-receptor family.

In essence, the physiological effects of natriuretic peptides are catalyzed through the classic intracellular second messenger cGMP, which activates cGMP-dependent protein kinases (PKG), cGMP-dependent phosphodiesterases (PDEs), and cyclic nucleotide-gated ion channels (CNGs) as effecter molecules (97–101). The resultant activation of these three effectors molecules (PKGS, PDEs and CNGs) elicits various physiological functions, namely: vasodilation, excretion of sodium and water, antiproliferation, and antihypertrophic effects (Fig. 2). On the other hand, it is considered that ANP binding to NPRC leads to hydrolysis of phosphoinositides and decrease in cAMP levels; however, their biological significance yet remains to be seen. Overall, the signaling of NPs and their receptors leads to combined physiological functions, which together provide renoprotection, cardioprotection, and vascular protection. However, more studies are needed to dissect out the role of specific physiological functions of NPs and their cognate receptors in the prevention of cardiovascular disease states.

Renal Action of Natriuretic Peptides

ANP action is perceived to facilitate the excretion of salt and water with an increase in glomerular filtration rate (3,102,103). Renal sites of ANP action include; inner mudulary collecting duct, glomerulus, and mesangial cells (104–108). The intracellular actions of ANP in renal cells include the stimulation of GC activity and reduction in adenylyl cyclase and phospholipase C activities, sodium influx, and reduced calcium concentrations (3,5,69). The increased production of cGMP at ANP concentrations affecting renal functions correlate with the effects of dibutyryl-cGMP, which prevents mesangial cell contraction in response to ANG II (109,110). The most compelling evidence supporting a role for cGMP in mediating the renal effects of ANP was obtained with selective NPRA antagonists, A71915 to eliminate the renal effect of infused ANP, including the elevation of urinary cGMP (111,112). These studies established that ANP effect in kidney is largely mediated by cGMP through the activation of NPRA. ANP markedly lowers renin secretion from kidney and also affects plasma renin concentrations (113–117). Ample experimental data have established that ANP plays an important role in regulation of renal function by its vasodilatory and natriuretic responses and its ability to counteract the renin-angiotensin-aldosterone system (RAAS) in a tissue-specific manner (118). Attempts have been made to define physiological responses in kidney by infusing the exogenous ANP (119). Although two compounds, A71917 and HS-140-1, have been shown to diminish the effect of ANP by antagonizing NPRA, however, these compounds do not completely inhibit NPRA activity (120–123). Activation of natriuretic peptides (ANP, BNP), enhances the pressure-natriuresis relationship and reduces atrial pressures. It has also been suggested that chloride-mediated feedback control of NPRA occurs in the kidney and plays a role in ANP-mediated natriuresis (124). Recent studies using ANP and NPRA gene-targeted mice have established that ANP/NPRA system suppresses renin-angiotensin system and decreases blood pressures (102,117,125,126).

Vascular Action of Natriuretic Peptides

The findings on the effect of ANP either in intact aortic rings or in cultured vascular smooth muscle cells have always reported an elevation in the intracellular levels of cGMP (127). The correlative evidence between ANP-induced cGMP accumulation and vasodilation has suggested the role of cGMP as the second messenger of dilator responses to ANP (3,128–

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130). ANP as well as cGMP analogs have been found to reduce the agonist-induced increases in cytosolic Ca^{2+} concentrations (131–133). It has been reported that cGMP activates sarcolemmal Ca^{2+} -ATPase, and this mechanism may be important in the ANP-induced decreases in cytosolic Ca^{2+} in vascular smooth muscle cells (134–136). Nevertheless, it is anticipated that the ultimate effect of ANP in vascular smooth muscle cells could be due to production of cGMP and the activation of cGMP-dependent protein kinases (130,133,137). However, more studies are needed to define the biochemical and molecular basis of NP actions in vascular smooth muscles cells.

Role of Natriuretic Peptides and their Receptors in Hypertension and other Pathophysiological Function

Studies with ANP-deficient genetic strains of mice demonstrated that a defect in the ANP synthesis can cause hypertension (138). The blood pressures of homozygous null mutant animals were elevated by 8–12 mmHg when they were fed with standard or intermediate salt diets. Heterozygous animals showed normal blood pressures and normal amount of circulatory ANP, however, they became hypertensive and blood pressure was elevated by 20–27 mmHg if these animals were fed with high salt diets (125,138,139). Those previous findings clearly demonstrated that genetically reduced production of ANP can lead to salt-sensitive hypertension. Transgenic mice overexpressing ANP, developed sustained hypotension with arterial pressure that was 25–30 mmHg lower than their nontrasgenic siblings (125,140,141). A previous study has also demonstrated that somatic delivery of ANP gene in spontaneously hypertensive rat (SHR) induced a sustained reduction of systemic blood pressure, raising the possibility of using ANP as therapeutic agent for treatment of human hypertension (142). The disruption of pro-ANP gene (Nppa) in mice also exhibits cardiac hypertrophy and exaggerated hypertrophic responses to pressure or volume overload (143–145).

Genetic mouse models with disruption of both ANP and NPRA genes have provided strong support for the role of NP hormone-receptor system in the regulation of arterial pressure and other physiological functions (102,117,125,139,146–152). Therefore, the genetic defects that reduce the activity of ANP and its receptor system can be considered as candidate contributors to essential hypertension (102,139,146,148,149,153–155). Interestingly, complete absence of NPRA causes hypertension in mice and leads to altered renin and ANG II levels, cardiac hypertrophy, and lethal vascular events similar to those seen in untreated human hypertensive patients (102,117,151,154,156). In contrast, increased expression of NPRA (corresponding to the increasing number of *Npr1* gene copies) reduces blood pressure and increases the second messenger cGMP (102,152).

Our recent studies have examined the quantitative contributions and possible mechanisms mediating the responses of varying numbers of *Npr1* (coding for NPRA) gene copies by determining the renal plasma flow, (RPF), glomerular filtration rate (GFR), urine flow, and sodium excretion patterns following blood volume expansion in *Npr1* homozygous null mutant (0-copy), wild-type (2-copy), and gene-duplicated (4-copy) mice in a *Npr1* gene-dose-dependent manner (102). These findings demonstrated that the ANP/NPRA axis is primarily responsible for mediating the renal hemodynamic and sodium excretory responses to intravascular blood volume expansion and established that NPRA is a hallmark receptor, which plays a critical role in mediating the natriuresis, diuresis, and renal hemodynamic responses to acute blood volume expansion. Interestingly, ANP/NPRA system inhibits aldosterone synthesis and release from adrenal glomerulosa cells (3,117,126,157) suggesting that this ANP action on aldosterone could be physiologically important, which probably accounts for renal natriuretic and diuretic effects. Furthermore, the studies with *Npr1* gene-disrupted mice demonstrated that at birth, the absence of NPRA allows greater renin and ANG II levels and increased renin mRNA expression compared with the wild-type mice (117). However, at 3–

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16 weeks of age, the circulating renin and ANG II levels were decreased dramatically in *Npr1* homozygous null mutant mice as compared with wild-type control mice. This decrease in renin activity in adult *Npr1* null mutant mice is implicated due to progressive elevation in arterial pressure leading to inhibition of renin synthesis and release from the kidney juxtaglomerular cells (102). It has been suggested that increased levels of ANP released into the plasma in response to blood volume expansion is the main mediator for natriuretic and diuretic responses (102,119,158).

The mechanistic role of ANP/NPRA system in counter-acting the pathophysiology of hypertension is still not well understood. Although, the expression of ANP and BNP is markedly increased in patients with hypertrophic or failing heart, it is unclear if the NP system is activated to play a protective role by reducing the detrimental effects of high blood pressure caused by sodium retention and fluid volume, inhibiting the renin-angiotensin-aldosterone system (RAAS) or it is simply a consequence of the hypertrophic changes occurring in the heart (102,153,156,159). Our findings have indicated that in newborn *Npr1* homozygous null mutant pups (2 days after birth), the intrarenal rein content was 2.5-fold higher than in 2-copy wild-type counterparts. However, the adult (16-weeks) hypertensive *Npr1* null mutant mice showed 50–70% reduction in plasma renin concentration and renal renin content as compared with wild-type control animals (117). In contrast, the adrenal renin contents and mRNA expression as well as ANG II and aldosterone levels were elevated in adult homozygous null mutant mice than wild-type mice (117,126). Together, the studies in both SHR and *Npr1* gene-knockout hypertensive mouse models suggest that in hypertension, both kidney and circulatory renin concentrations are decreased, however, as a compensatory event, the adrenal renin is increased (117). Thus in light of those previous findings, it can be suggested that ANP/NPRA system may play a key regulatory role in the synthesis and maintenance of both systemic and tissue levels of RAAS components in both physiological and pathological conditions.

The disruption of *Npr1* gene indicated that the blood pressure of homozygous mutant mice remained elevated and unchanged in response to either minimal or high salt diets (150). These investigators suggested that NPRA may exert its major effect at the level of vasculature and probably does so independently of salt. In contrast, Oliver et al., (152) reported that disruption of *Npr1* gene resulted in chronic elevation of blood pressure in mice fed with high salt diets. The fact that adrenal ANG II and ALDO levels are increased in *Npr1* gene-disrupted mice may explain the elevated systemic blood pressure with decreasing *Npr1* gene-copy numbers (126). However, on the other hand, adrenal ANG II and ALDO levels are decreased in *Npr1* gene-duplicated mice. A low-salt diet stimulated adrenal ANG II and ALDO levels in all *Npr1* gene-targeted (gene-disrupted and gene-duplicated) mice, whereas a high-salt diet suppressed adrenal ANG II and ALDO levels in *Npr1* gene-disrupted mice and wild-type mice, but not in *Npr1* gene-duplicated mice. Our findings suggest that NPRA signaling has a protective effect against high-salt in *Npr1* gene-duplicated mice as compared with *Npr1* gene-disrupted mice (126). Indeed, more studies are needed to clarify the relationship between salt-sensitivity and blood pressures in *Npr1* gene-targeted mice.

In addition to ANP and NPRA, other natriuretic peptides and their cognate receptors have also been implicated to play roles in hypertension and cardiovascular regulation along with some other physiological and pathophysiological functions (Table II). It has been shown that BNP homozygous null mutant mice develop pressure-sensitive ventricular fibrosis; however, these mice do not show an increased blood pressure or hypertension as compared with the wild-type mice (160). The genetic-disruption of CNP in mice exhibits dwarfism, and homozygous null mutant mice die in early age due to an abnormal endochondral ossification (161). On the other hand, the overexpression of CNP in cardiomyocytes of transgenic mice prevented cardiac hypertrophy induced by myocardial infarction (162). It has been reported that the *Npr2* homozygous null mutant mice exhibit dwarfism (163). However, intriguing was the finding

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that a spontaneous mutation, which results in the substitution of leucine with arginine in GC catalytic domain of NPRB, also exhibits dwarfism in mice (164). Furthermore, homozygous loss of function mutation of *Npr2* gene in humans has been shown to be linked with impaired skeletal growth and to cause acromesomelic dysplasia, type Marteaux (AMDM) (165). The *Nrp3* homozygous null mutant mice show reduced ability to concentrate urine and exhibit long bone overgrowth and abnormal growth of chondrocytes (166). Interestingly, recessive loss of function mutation of *Npr3* gene leads to skeletal overgrowth and lack of body fat deposition in mutant mice (167).

Role of Natriuretic Peptides and their receptors in Cardiovascular Events

High levels of endogenous ANP are thought to compensate the condition of patients with heart failure by reducing preload and after load. Evidence suggests that a high plasma ANP/BNP level is a prognostic predictor in humans with heart failure (168–170). In patients with severe congestive heart failure (CHF), the concentrations of both ANP and BNP increase higher than control values, however, the BNP concentration increases 10- to 50-fold higher than a comparative increases in ANP concentrations (30). These findings indicated that ANP and BNP elicit distinct physiological and pathophysiological effects. Interestingly, the half-life of BNP is greater than ANP, thus the evaluation of the diagnostic importance of the NPs have favored BNP (171). The inactive N-terminal fragment of BNP (NT-proBNP) has even a greater half-life than the BNP. The plasma levels of both BNP and NT-proBNP are markedly elevated under the pathophysiological condition of cardiac dysfunction, including diastolic dysfunction, congestive heart failure, and pulmonary embolism (171–174). The basal plasma levels of BNP vary from 5–50 pg/ml and NT-proBNP levels ranges from 7–160 pg/ml. An abnormal range is considered as 100 pg/ml for BNP and 125 pg/ml for NT-proBNP (172). Nevertheless, the secretion of both ANP and BNP from ventricular myocytes increases proportionally in relation to the magnitude of dysfunction or disease states (175). Increased ventricular expression of ANP and BNP in *Npr1* null mutant mice has been shown to be proportionalely related with cardiac hypertrophy and fibrosis (154,176). It has been suggested that ventricular expression of ANP and BNP is more closely associated with local cardiac hypertrophy and fibrosis than plasma ANP levels and systemic blood pressure (176). It has been reported that BNP can be considered a as an important prognostic indicator in CHF patients, however, NT-proBNP is considered to be a stronger risk bio-indicator for cardiovascular disorders (177). Nevertheless, both BNP and NT-proBNP can provide an ideal tool to be utilized as blood tests to diagnose cardiovascular disorders in high risk CHF patients. BNP and NT-proBNP have also been used as biological markers in patients with chronic kidney disease with left ventricular hypertrophy and coronary artery disease (178). Similarly, the levels of both BNP and NT-proBNP are also greatly increased in patients with renal insufficiency. The BNP level is increased to almost 200 pg/ml and NT-proBNP levels reaches to approximately 1200 pg/ml in patients with reduced creatinin clearance (179,180).

Although, the circulating BNP levels are far less than that of ANP levels in normal subjects, the increase in BNP concentrations in plasma can surpass the level of ANP in patients with CHF (30,181,182). Nevertheless, it is widely believed that ANP and BNP concentrations are markedly increased both in cardiac tissues and in plasma of CHF patients (169–171). Studies in patients with chronic CHF have suggested that the plasma NPs levels decrease, whereas plasma cGMP levels increase significantly from femoral artery to the femoral vein, however, in patients with mild CHF, the plasma cGMP level correlated with ANP level (168). Furthermore, these authors suggested that among patients with severe CHF, plasma cGMP levels reached a plateau despite high levels of plasma ANP, and the molar ratio of cGMP production to ANP in peripheral circulation was significantly lower than those in patients with mild congestive heart failure. The findings of those previous studies further indicated that down-regulation of NPRA may also occur in the peripheral vascular bed of patients with

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chronic severe congestive heart failure. In hypertrophied heart, ANP and BNP genes are overexpressed, suggesting that autocrine and/or paracrine effects of these natriuretic peptides, predominate and might serve as an endogenous protective mechanism against maladaptive pathological cardiac hypertrophy (153,176,183–186). Inactivation of either ANP or *Npr1* gene in mice increases the cardiac mass to a great extent (139,151,154,156,176,187–189).

Previous studies have demonstrated that *Npr1* gene-disruption in mice provokes enhanced expression of hypertrophic marker genes, pro-inflammatory cytokines, and activation of matrix metalloproteinases and nuclear factor-kappa B(NF-kB) associated with cardiac hypertrophy, fibrosis, and extracellular matrix remodeling (156,190,191). The disruption of *Npr1* gene also leads to a dramatic reduction in testosterone production in Leydig cells (146). Furthermore, the sarcolemal/endoplasmic reticulum Ca^{2+}-ATPase-2a (SERCA-2a) progressively decreased in the hypertrophied hearts of *Npr1* homozygous null mutant mice as compared with wild-type control mice (156). It has been implicated that deficiency of NPRA leads to enhanced expression of angiotensin converting enzyme and ANG II receptor type A (AT1a) in *Npr1* null mutant mice (154). Morevover, it has also been suggested that *Npr1* antagonizes AT1 a receptor-mediated cardiac remodeling and provides an endogenous protective mechanism in the heart (154,192,193). Interestingly, cardiomyocyte restricted loxP/Cre-mediated inactivation of *Npr1* gene in mice (CMGC-A knockout mice) resulted in local ablation of ANP effect in the heart, which was accompanied by an increase in cardiomyocyte size and expression of cardiac hypertrophy marker genes (194). Furthermore, cardiomyocytes of CMGC-A knockout mice as well as conventional *Npr1* gene-disrupted mice exhibited enhanced ANG II-dependent Ca^{2+} levels and increased activation of Na^{+}/H^{+} exchanger (195,196). In addition, studies with both smooth muscle and endothelial specific *Npr1* knockout mice have shown that arteries from these mice exhibit higher sensitivity to endothelial nitric oxide and significant arterial hypertension (197,198). Moreover, it has also been suggested that *Npr1* gene represents a potential locus for susceptibility to atherosclerosis and cardiac hypertrophy (199). The disruption of *Npr2* gene showed impairment of endothelial ossification and developmental defects of female gonad (163). However, the blood pressure was not different in *Npr2* null mutant mice as compared with the wild-type control mice. Since, the *Npr2* null mutant mice die prematurely due to severe skeletal malformation, their cardiovascular phenotype has not been well characterized. Interestingly, using dominant negative mutant of NPRB, transgenic rats have been produced, which exhibited selective reduction in NPRB signaling without any effect on NPRA. The NPRB-dominant negative transgenic rats exhibit increased heart rate and blood pressure-independent cardiac hypertrophy (200).

A significant inverse relationship has been found between myocardial ANP and BNP expression levels and increases in left ventricular cardiac mass (172,201). Those previous findings suggested that NPs expression plays a protective role in hypertrophied heart. It has also been shown that functional alterations of ANP promoter are linked to cardiac hypertrophy in progenies of crosses between Wistar Kyoto (WKY) and Wistar Kyoto-derived hypertensive and a single nucleotide polymorphism can alter the transcriptional activity of ANP gene promoter (WKYH) rats (202,203). Together, it is implicated that ANP/NPRA system may protect cardiomyocytes against hypertrophy as a strong candidate gene for the determination of left ventricular mass (156,176,190,203).

Conclusions

Till to date, three related natriuretic peptides and three distinct receptors have advanced our knowledge towards understanding of the control of high blood pressure, hypertension, and cardiovascular disorders to a great extent. The development of gene-knockout and gene-duplication mouse models along with transgenic mice have provided a framework for understanding both the physiological and pathophysiological importance of NPs and their

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receptors and the signaling pathways involved in their mechanisms of action in hypertension and cardiovascular events. Although, a considerable progress has been made, the transmembrane signaling mechanisms of NPs and their receptors are still not well understood. Future challenges will include; the identification and characterization of cellular targets as well as the roles of NPs and second messenger cGMP in gene transcription, cell growth, apoptosis, and differentiation. More vigorous studies on the crosstalk with other signaling mechanisms needs to be pursued systematically. Now, NPs and their receptors are considered as circulating markers of congestive heart failure, however, their therapeutic potential for the treatment of cardiovascular diseases such as hypertension, renal insufficiency, cardiac hypertrophy, congestive heart failure, and stroke is still lacking. Indeed, alternative avenues of investigations need to be undertaken, as we are at the initial stage of the molecular therapeutic and pharmacogenomic implications of natriuretic peptides and their receptor systems.

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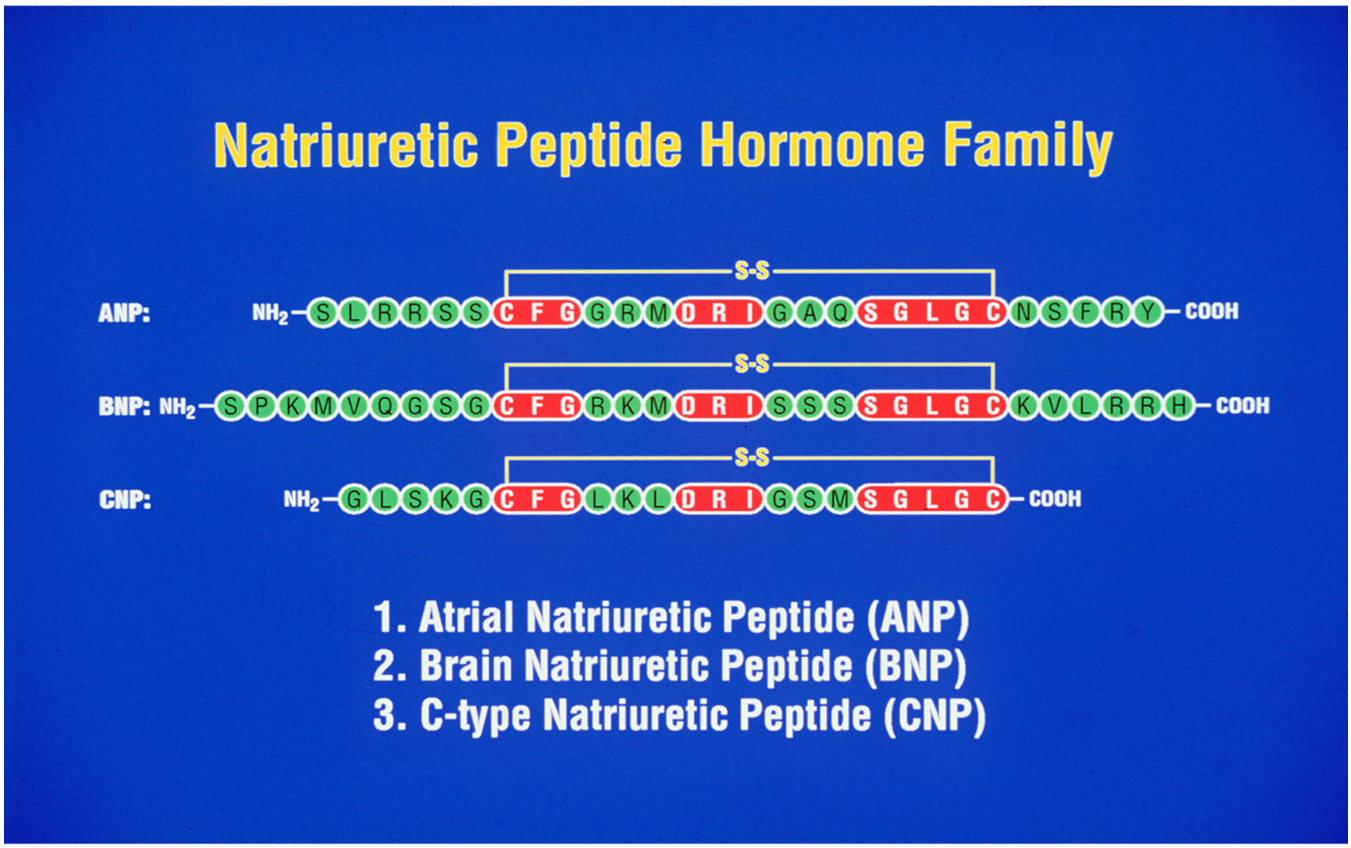

Figure 1. Natriuretic peptide hormone family

Amino-acid sequence and comparison of human ANP, BNP, and CNP with conserved residues represented by red boxes. The lines between two cysteine residues in ANP, BNP, and CNP molecules indicate a 17-amino acid disulfide bridge, which is essential for the biological activity of these peptide hormones.

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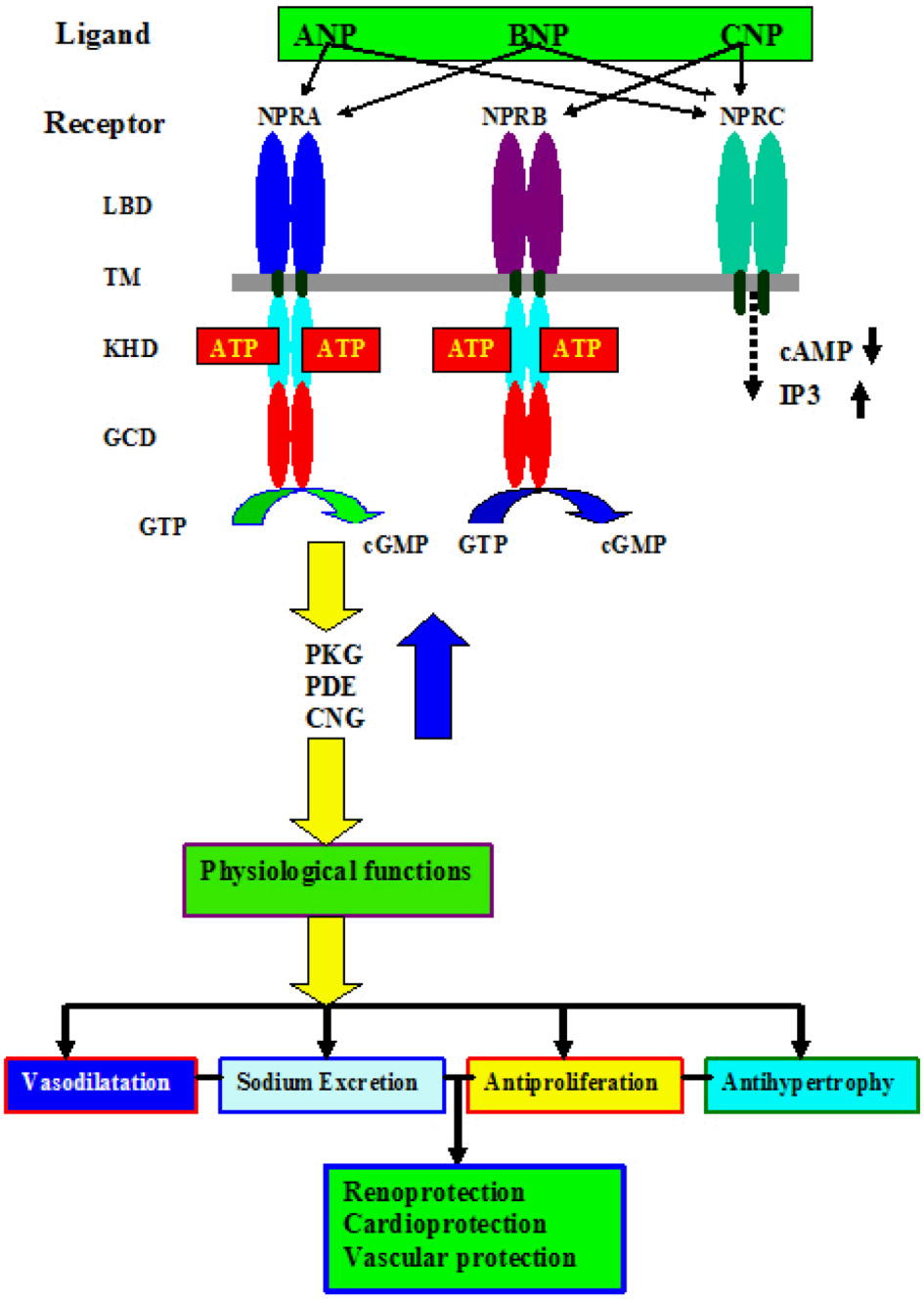

Figure 2. Diagramatic representation of ligand specificity, transmembrane topology and signaling system of natriuretic peptide receptor-A, -B, and -C (NPRA, NPRB, and NPRC), respectively

The arrows indicate the specificity of ligand to specific NPs receptor. The extracellular ligand binding domain (LBD), transmembrane region, and intracellular protein kinase-like homology domain (KHD) and guanylyl cyclase catalytic domain (GCD) of NPRA and NPRB are indicated. Similarly, ligand binding domain, transmembrane region, and short intracellular tail of NPRC are also indicated. Both NPRA and NPRB are shown to bind ATP in protein-KHD and to generate second messenger cGMP from GTP hydrolysis. An increased level of intracellular cGMP stimulates and activates three known cGMP effecter molecules namely; cGMP-dependent protein kinases (PKGs), cGMP-dependent phosphodiesterases (PDEs), and

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cGMP-gated or cyclic nucleotide gated-ion channels (CNGs). The activation of PKGs, PDEs, and/or CNGs elicits physiological responses including: vasodilation, sodium and water excertion, antiproliferation, and antihypertrophic effects. One or more specific physiological responses lead to renoprotection, cardioprotection and/or vasoprotection. ANP binding to NPRC has been suggested to increase inositoltrisphosphate (IP3) and to decrease cAMP levels in target tissues and cells.

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TABLE 1

Various plasma membrane forms of guanylyl cyclase/natriuretic peptide receptors with respective ligands and prominent tissue distribution.

Ligand	Guanylyl Cyclase/ Natriuretic peptide Receptor	Tissue-Specific Distribution
ANP/ANF	GC-A/NPRA	Kidney, adrenal glands, heart, lung, vascular bed, ovary, testis, brain, and other tissues
BNP	GC-A/NPRA	Kidney, adrenal glands, heart, lung, vascular bed, ovary, testis, brain, and other tissues
CNP	GC-B/NPRB	Vascular bed, fibroblast, heart, lung adrenal gland, brain, chondrocytes and bones,and other tissues
Guanyly and Uroguanylyn/ Enterotoxin	GC-C	Colon, intestine, and kidney
Orphan	GC-D	Olfactory neuroepithelium
Orphan	GC-E	Retina, pineal gland
Orphan	GC-F	Retina
Orphan	GC-G	Skeletal muscle, lung, intestine, and kidney
Calcium-binding proteins	ROS-GC	Rod outer segment
Orphan	GC-Y-X1	Sensory neurons of C elegans
NO, CO	Soluble Cyclase	Smooth muscle, platelet, kidney, lung and other tissues

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TABLE II

Nomenclature of peptides/proteins and genes of natriuretic peptides and their receptors. The disease-specific phenotypes of gene-disrupted mice of natriuretic peptides and their receptors have been presented.

Peptide/Protein Nomenclature	**Gene Nomenclature**	**Gene-disrupted Phenotype in Mouse**
ANP/ANF	*Nppa*	High blood pressure, cardiac hypertrophy (Ref. (139,143,145)
BNP	*Nppb*	Vascular complication, fibrosis (Ref. (160)
CNP	*Nppc*	Dwarfism, reduced bone growth, impaired endochondral ossification (Ref. (161)
NPRA	*Npr1*	Volume overload, high blood pressure, hypertension, cardiac, hypertrophy, cardiac fibrosis and inflammation, and reduced testosterone levels (Ref. 102,146,147,151,153,154,156,190)
NPRB	*Npr2*	Seizures, dwarfism, female sterility, decreased adiposity (Ref. (163,164,165)
NPRC	*Npr3*	Bone deformation with long bone overgrowth (Ref. 166,167)