HHS Public Access

Author manuscript

Handb Exp Pharmacol. Author manuscript; available in PMC 2016 May 04.

Published in final edited form as:

Handb Exp Pharmacol. 2009 ; (191): 341–366. doi:10.1007/978-3-540-68964-5_15.

Natriuretic Peptides: Their Structures, Receptors, Physiologic Functions and Therapeutic Applications

Lincoln R. Potter, **Andrea R. Yoder**, **Darcy R. Flora**, **Laura K. Antos**, and **Deborah M. Dickey**

Abstract

Natriuretic peptides are a family of three structurally related hormone/paracrine factors. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are secreted from the cardiac atria and ventricles, respectively. ANP signals in an endocrine and paracrine manner to decrease blood pressure and cardiac hypertrophy. BNP acts locally to reduce ventricular fibrosis. C-type natriuretic peptide (CNP) primarily stimulates long bone growth but likely serves unappreciated functions as well. ANP and BNP activate the transmembrane guanylyl cyclase, natriuretic peptide receptor-A (NPR-A). CNP activates a related cyclase, natriuretic peptide receptor-B (NPR-B). Both receptors catalyze the synthesis of cGMP, which mediates most known effects of natriuretic peptides. A third natriuretic peptide receptor, natriuretic peptide receptor-C (NPR-C), clears natriuretic peptides from the circulation through receptor-mediated internalization and degradation. However, a signaling function for the receptor has been suggested as well. Targeted disruptions of the genes encoding all natriuretic peptides and their receptors have been generated in mice, which display unique physiologies. A few mutations in these proteins have been reported in humans. Synthetic analogs of ANP (anaritide and carperitide) and BNP (nesiritide) have been investigated as potential therapies for the treatment of decompensated heart failure and other diseases. Anaritide and nesiritide are approved for use in acute decompensated heart failure, but recent studies have cast doubt on their safety and effectiveness. New clinical trials are examining the effect of nesiritide and novel peptides, like CD-NP, on these critical parameters. In this review, the history, structure, function, and clinical applications of natriuretic peptides and their receptors are discussed.

1 History of Natriuretic Peptides

Key cell biological observations that predicted the existence of natriuretic peptides were reported over fifty years ago. Kisch initially found that atrial, but not ventricular, cells contained highly developed Golgi networks, similar to those observed in secretory cells (Kisch 1956). Jamieson and Palade reported that atrial, but not ventricular, myocytes contain spherical, electron opaque granules (Jamieson and Palade 1964). At the same time, physiological experiments conducted by Henry and colleagues revealed that balloon distension of the atria correlated with increased urination in dogs (Henry et al. 1956). In the late 1960s, de Bold and colleagues began characterizing the atrial granules. They found that the content of the granules changed in response to alterations in electrolyte and water

L.R. Potter, Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota – Twin, Cities, 321 Church St SE, Minneapolis, MN 55455, USA, pottter@umn.edu.

balance (de Bold et al. 1981). In a seminal study published in 1981, de Bold and colleagues elegantly linked the seemingly disparate studies of Kisch and Henry by showing that atrial, but not ventricular, extracts contain a potent blood pressure decreasing component that works by stimulating renal sodium and water secretion (de Bold et al. 1981). Thus, the first natriuretic peptide was discovered.

Shortly after the publication of this landmark paper, a number of groups reported the purification and sequencing of atrial peptides of varying sizes that possessed natriuretic, diuretic, and/or smooth muscle relaxing activity (Currie et al. 1984; Flynn et al. 1983; Kangawa et al. 1984; Misono et al. 1984). Several different names were given to these peptides such as atrial natriuretic factor, atriopeptin, cardionatrin, and cardiodilatin. However, atrial natriuretic peptide (ANP) is most often used to describe this peptide in the current literature. The second member of the family to be discovered, B-type natriuretic peptide (BNP), was originally called brain natriuretic peptide because it was purified and sequenced from porcine brain (Sudoh et al. 1988). However, subsequent studies found that it is more highly concentrated in cardiac ventricles of patients with heart failure (Mukoyama et al. 1991; Mukoyama et al. 1990). Therefore, it is often described as B-type natriuretic peptide today. Finally, the third member of the family, C-type natriuretic peptide (CNP) (Sudoh et al. 1990) was purified in 1991 from porcine brain extracts based on its ability to relax smooth muscle. All three members are similar in primary amino acid structure, contain a 17-residue disulfide ring, and are the products of separate genes.

2 Natriuretic Peptides

2.1 Atrial Natriuretic Peptide

All natriuretic peptides are synthesized as preprohormones (Fig. 1). The human gene encoding ANP is called *NPPA* (GeneID 4878) and is located on chromosome 1 at location 1p36.21. *NPPA* is approximately 2 Kb in length and consists of 3 exons and 2 introns. The resulting mRNA gives rise to a 151 amino acid polypeptide, known as preproANP. The first 25 amino acids constitute a signal sequence that is cleaved to yield a 126 amino acid peptide called proANP, which is the major form of ANP stored in the atrial granules (Oikawa et al. 1984). Upon release from these granules, proANP is rapidly cleaved by corin, a transmembrane cardiac serine protease. Corin is highly expressed on the extracellular surface of atrial cardiomyocytes and has been shown to cleave proANP into the biologically active 28-amino acid form of ANP in vitro (Yan et al. 2000). Mice lacking functional corin have dramatically reduced levels of fully processed ANP in their hearts and are mildly hypertensive (Chan et al. 2005). Alternative processing of proANP in the kidney by an unknown protease results in a 32-amino acid peptide called urodilatin that contains four additional amino-terminal residues (Forssmann et al. 1998). Disruption of the murine ANP gene, *Nppa*, results in marked hypertension, which was initially described as salt-sensitive (John et al. 1995), but later found not to be correlated with dietary salt intake (John et al. 1996).

ANP is well conserved between species (Fig. 2). The 28-amino acid mature form of ANP in humans and rats differs by only one amino acid at position 12, where the human peptide contains a methionine and the rat peptide contains an isoleucine. The mature, circulating

form of ANP is identical in humans, chimps, dogs, pigs, horses, and sheep. The sequence of mature rat ANP is identical in mice and rabbits. Additionally, the entire length of the preproANP polypeptide, not just the carboxyl terminal biologically active end, is well conserved. The preproANP polypeptide is similar in many mammalian species, with 100, 86, 81, and 81% homology to the human form in chimpanzees, dogs, mice, and rats, respectively [NCBI Homologene Database].

Several polymorphisms within the *NPPA* coding region have been identified. The T2238C SNP [NCBI SNP Database #rs5065] falls within the coding region and results in a missense mutation that changes the stop codon of preproANP to an arginine, resulting in a preproANP that has two extra arginine residues on the C-terminal end. This same double-arginine pattern is present in the wild-type murine and rat preproANP, but the mature circulating peptide lacks these two residues. It is not known whether individuals with this polymorphism have circulating ANP that is 30-amino acids in length or if these two arginine residues are cleaved during processing as seen in mice and rats. Three other SNPs cause missense mutations in the same region of preproANP (rs5063, rs13305987, and rs3170926), resulting in V32M, A70V, and L77F substitutions, respectively. This section of proANP is cleaved upon atrial release, and thus the mature circulating form of ANP is not affected. One relatively rare SNP in the Entrez SNP database (rs1803268) causes an arginine to glutamic acid substitution at position 126 of preproANP, which results in a sequence change at the fourth position of the mature 28 residue peptide. The effect of this mutation on ANP function has not been described.

Release of proANP from the atrial granules is primarily stimulated by stretch of the atrial wall caused by increased intravascular volume (Bilder et al. 1986; Edwards et al. 1988; Lang et al. 1985), but pressor hormones also stimulate ANP release (Ruskoaho 2003). Upon secretion and cleavage into the mature peptide, ANP enters the coronary sinus and is distributed to its target organs via the circulation. Plasma levels of ANP are relatively low (10fmol ml^{-1}), but in patients with congestive heart failure, circulating ANP levels are elevated from 10- to 30-fold (Burnett et al. 1986; Cody et al. 1986).

The plasma half-life of ANP in humans is approximately 2 min, with reported values falling between 1.7 and 3.1 min (Nakao et al. 1986; Yandle et al. 1986). Degradation of the active ANP peptide occurs through the actions of neutral endopeptidase (NEP) (Stephenson and Kenny 1987; Vanneste et al. 1988) as well as through binding to the natriuretic peptide clearance receptor (NPR-C). NPR-C is a cell surface receptor that lacks guanylyl cyclase activity and controls the local concentrations of natriuretic peptides via constitutive receptor mediated internalization and degradation (see below). Inhibiting NEP, increases the half-life of ANP both in vitro (Stephenson and Kenny 1987; Yandle et al. 1989) and in vivo (Yandle et al. 1989), suggesting that NEP activity contributes to the rapid clearance of ANP. However, it is important to note that mice lacking functional NEP do not exhibit increased natriuretic peptide function (Lu et al. 1995). In contrast, mice lacking NPR-C are hypotensive, exhibit skeletal overgrowth and have reduced ability to clear ANP compared to wild type mice, suggesting that NPR-C is also a physiologic regulator of circulating natriuretic peptide concentrations (Matsukawa et al. 1999).

2.2 B-Type Natriuretic Peptide

BNP was initially purified and sequenced from extracts of porcine brain tissue and hence it was named “brain natriuretic peptide” (Sudoh et al. 1988). Subsequently, BNP was found at much higher concentrations in cardiac tissues (Mukoyama et al. 1991; Mukoyama et al. 1990). The gene encoding human BNP, *NPPB* (GeneID 4879), is located on chromosome 1 at 1p36.2. In the mouse genome, *Nppb* is located on chromosome 4 (Ogawa et al. 1994a). Like *NPPA*, the *NPPB* gene consists of 3 exons and 2 introns (Ogawa et al. 1994a). PreproBNP is 134 amino acids in length, consisting of a 26 amino acid signal sequence followed by 108 amino acids that constitute proBNP. Unlike preproANP, which has high species homology throughout the entire polypeptide sequence, preproBNP sequences in mammals only have high homology at the amino and carboxyl terminal ends of the polypeptide. For example, the homology of canine preproBNP to human preproBNP is 53%, whereas the homology for preproANP between these species is 85%. This lower level of homology gives rise to differing lengths of the active, circulating BNP between mammalian species. For example, in humans and pigs circulating BNP is 32 amino acids in length, while in rats and mice the circulating form is 45 amino acids. The peptidase that cleaves proBNP to its active form has not been identified, but corin is a reasonable suspect.

There are several polymorphisms found in the coding region of human *NPPB* reported in the SNP database. Two, rs35690395 and rs35628673, result in synonymous amino acid residues. Four other SNPs result in changes in the sequence of preproBNP. One (rs5227) results in an R25L substitution of one amino acid before the signal cleavage site. Another mutation (rs5229) results in an R to H substitution at position 47 in the preprohormone sequence, which is the 21st amino acid of proBNP. Mutation rs5230 changes an M to an L at position 93 in preproBNP, corresponding to the 67th amino acid in proBNP. Mutation rs35640285 results in a V to F change at position 94, which is the 68th amino acid of proBNP. None of the above SNPs create changes in the sequence of the mature circulating 32 amino acid form of BNP.

Although low levels of BNP are stored with ANP in atrial granules, BNP is found at greater concentrations in cardiac ventricles. In this tissue, BNP is not stored in granules, but rather transcribed as needed in response to cardiac stress states such as volume overload. The transcription of BNP is under the regulatory control of GATA4, a transcription factor (Grepin et al. 1994; Thuerauf et al. 1994). In normal human subjects, plasma concentrations of BNP are very low (1 fmol ml-1), but in response to congestive heart failure, circulating concentrations of BNP are dramatically elevated (Mukoyama et al. 1991; Mukoyama et al. 1990).

Compared to ANP, circulating BNP has a significantly longer half-life of around 20 min in humans (Mukoyama et al. 1991; Mukoyama et al. 1990). Unlike ANP, BNP is not initially cleaved by NEP. Instead, the first six amino-terminal amino acids of BNP are first cleaved by the metalloprotease, meprin A in the kidney brush border, which then allows further degradation by NEP (Pankow et al. 2007). Like all natriuretic peptides, BNP is also cleared from the circulation by NPR-C.

Both knockout and overexpression models of *Nppb* have been generated in mice. The knockout model of *Nppb* was created by targeted deletion of exons 1 and 2 (Tamura et al. 2000). In contrast to ANP knockout mice, $Nppb^{-/-}$ mice showed no signs of systemic hypertension or ventricular hypertrophy on standard or high salt diets. However, $Nppb^{-/-}$ mice had ventricular fibrotic lesions that increased in size and number in response to pressure overload, compared to wild type animals. Thus, these studies suggest that BNP is not a regulator of blood pressure, at least in mice. Rather, it is a paracrine regulator of cardiac remodeling. In murine overexpression models of BNP, blood pressure reduction of 20 mmHg was seen with 10- to 100-fold increases in plasma BNP levels (Ogawa et al. 1994a). Interestingly, these mice had marked increases in long bone length compared to their wild-type littermates, which most likely resulted from overactivation of NPR-B, the receptor of CNP (see Sect. 2.3).

2.3 C-Type Natriuretic Peptide

C-type natriuretic peptide (CNP) was initially purified and sequenced from porcine brain extracts (Sudoh et al. 1990). It is the most highly expressed natriuretic peptide in the brain but is also highly expressed in chondrocytes and endothelial cells. Unlike ANP and BNP, the human gene encoding CNP, *NPPC* (GeneID 4880), is not located on chromosome 1 but on chromosome 2 at location 2q24-qter (Ogawa et al. 1994b). Another difference of NPPC is that it consists of only 2 exons and 1 intron. In the murine genome, *Nppc* is also separated spatially from both ANP and BNP being located on chromosome 2 (Ogawa et al. 1994b). NPPC encodes a polypeptide of 126 amino acids, with a 23 amino acid signal sequence followed by a 103 amino acid proCNP (Tawaragi et al. 1991). PreproCNP shows remarkable homology between species, even more so than preproANP. The preproCNP polypeptides of mammalian species show 99, 96, 91, and 94% homology to the human form in chimpanzees, dogs, mice, and rats, respectively. Perhaps even more telling is that the circulating 22 amino acid carboxyl terminal form of CNP is absolutely identical in all of the above species.

Processing of proCNP to its mature form may occur through the action of the intracellular serine endoprotease, furin. In vitro, furin cleaves the 103 amino acid proCNP into a 53 amino acid carboxyl-terminal biologically active peptide (Wu et al. 2003). This 53 amino acid form of CNP (CNP-53) is the major active form of CNP, at the tissue level (Brown et al. 1997). However, in the systemic circulation, a shorter 22 amino acid form dominates (CNP-22). The protease responsible for this cleavage is not known. Importantly, CNP-53 and CNP-22 appear to bind and activate their cognate receptor, NPR-B, equally well (Yeung et al. 1996).

Within the coding region of NPPC, 4 polymorphisms are reported in the NCBI database, one of which (rs5266) is a synonymous mutation. The G58R SNP (rs13305993) falls in a region of preproCNP that is cleaved during maturation of the polypeptide. The R82Q and A83E polymorphisms (rs5267 and rs13305994) are on the amino terminal side of CNP-53 and would be cleaved upon conversion to CNP-22.

CNP is not stored in granules and its secretion is increased by growth factors (Suga et al. 1993; Suga et al. 1992b) and sheer stress (Chun et al. 1997) in cultured endothelial cells. CNP expression in neointimal vascular smooth muscle cells is increased in response to

vascular injury (Brown et al. 1997). In normal human subjects, mean CNP concentration is very low (1 fmol/ml). It is elevated in patients with congestive heart failure, although to a much lower extent than ANP and BNP (Charles et al. 2006; Del Ry et al. 2005; Kalra et al. 2003).

The clearance of CNP-22 in human plasma is very rapid, with a calculated half-life of 2.6 min (Hunt et al. 1994). Like ANP, CNP has been shown in vitro to be inactivated by neutral endopeptidase (Kenny et al. 1993) and is internalized and degraded by NPR-C. The NPR-C route of CNP degradation is especially important at the tissue level, as can be seen in NPR-C knockout models. Mice lacking functional NPR-C receptors have disproportionately long bones, most likely due to the failed clearance of CNP from specific regions in the growth plate (Jaubert et al. 1999; Matsukawa et al. 1999).

Both over and under expression models of CNP have been created in mice. Knockout animals were generated by disruption of exons 1 and 2 of *Nppc* (Chusho et al. 2001). The $Nppc^{-/-}$ mice are dwarfs due to impaired endochondral ossification and have severely reduced life spans. Targeted expression of CNP in the growth plate chondrocytes rescued the skeletal defect of $Nppc^{-/-}$ mice and prolonged their survival. Importantly, the *Nppc* transgene partially rescued skeletal growth in a murine model of achondroplasia caused by a gain of function mutation in the fibroblast growth factor receptor 3 ($Fgfr3^{ach}$), which accounts for most types of human dwarfism and may indicate that CNP analogs could be used to treat various forms of human dwarfism (Yasoda et al. 2004). A recent spontaneous point mutation in *Nppc* was characterized by a dwarfism phenotype similar to that seen in the $Nppc^{-/-}$ mice (Jiao et al. 2007). The mutation resulted in a missense mutation (R117G) in proCNP, which is one of the highly conserved residues in the cysteine ring found in all natriuretic peptides. Our recent data indicate that the mutant CNP has reduced ability to bind and activate NPR-B (Yoder, 2008). Finally, balanced translocations of chromosome 2, which separate putative negative transcriptional regulators from the CNP promoter, cause abnormal elevations in CNP and associated Marfornoid-like skeletal overgrowth in humans (Bocciardi et al. 2007; Moncla et al. 2007). Hence, moderate elevations of CNP are correlated with demonstrative skeletal overgrowth.

3 Natriuretic Peptide Receptors

There are three known natriuretic peptide binding proteins. All members contain a relatively large (~450 amino acid) extracellular ligand binding domain and a single membrane-spanning region of about 20 residues. Natriuretic peptide receptors A and B contain an equally large intracellular domain consisting of a so-called kinase homology domain, dimerization domain, and carboxyl-terminal guanylyl cyclase domain. Thus, NPR-A and NPR-B signal by catalyzing the synthesis of the intracellular signaling molecule cGMP. In contrast, NPR-C only contains a 37 residue intracellular domain and lacks guanylyl cyclase activity. It primarily controls local natriuretic peptide concentrations via receptor-mediated internalization and degradation, although many groups have reported signaling functions for NPR-C as well (Rose and Giles 2008).

3.1 Natriuretic Peptide Receptor-A

Natriuretic peptide receptor-A (NPR-A) is the principal receptor of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Its extracellular domain contains three intramolecular disulfide bonds and five N-linked glycosylation sites (Miyagi and Misono 2000; Miyagi et al. 2000). NPR-A exists as a homodimer or homotetramer in its native state, and oligomerization is ligand-independent (Chinkers and Wilson 1992; Iwata et al. 1991), although ligand binding does bring the juxtamembrane regions of each monomer closer together (Labrecque et al. 2001). NPR-A binds natriuretic peptides at a stoichiometry of 2:1 with a rank natriuretic peptide preference of: ANP $\geqslant$ BNP $\gg$ CNP (Bennett et al. 1991; Koller et al. 1991; Suga et al. 1992a). The human NPR-A gene is located on chromosome 1q21–22 and consists of 22 exons and 21 introns within 16 kilobases (Lowe et al. 1990; Takahashi et al. 1998). The murine NPR-A gene, *Npr1*, is located on chromosome 3.

Under basal conditions, NPR-A is phosphorylated on four serine and two threonine residues located in the N-terminal portion of the kinase homology domain (Potter and Hunter 1998b). Phosphorylation is essential for activation of NPR-A and dephosphorylation is a mechanism of desensitization in response to prolonged ANP exposure or protein kinase C activation (Potter and Garbers 1992, 1994). Although ATP increases ANP-dependent guanylyl cyclase activity, the mechanism for this effect is debatable (Antos et al. 2005; Antos and Potter 2007; Burczynska et al. 2007; Joubert et al. 2005). Our recent data indicate that ATP reduces the K_m for NPR-A (Antos and Potter 2007). NPR-A internalization and degradation is also controversial. One group consistently reports that the majority of internalized ANP-NPR-A complexes are degraded via a lysosomal pathway with a small portion returning intact to the plasma membrane (Pandey 2002). Meanwhile, studies in primary kidney, Chinese Hamster ovary, and HEK293 cells indicate that NPR-A is a membrane resident protein that does not undergo acute internalization and degradation (Fan et al. 2005; Koh et al. 1992; Vieira et al. 2001).

NPR-A and/or its mRNA is expressed in kidney, lung, adipose, adrenal, brain, heart, testis, and vascular smooth muscle tissue (Goy et al. 2001; Lowe et al. 1989; Nagase et al. 1997; Wilcox et al. 1991). NPR-A null mice exhibit chronic salt-resistant hypertension and cardiac hypertrophy and fibrosis (Kuhn et al. 2002; Lopez et al. 1995; Oliver et al. 1997). A deletion in the human NPR-A gene was identified in nine Japanese individuals, of which eight had essential hypertension; the normotensive individual with the altered allele had left ventricular hypertrophy (Nakayama et al. 2000). To our knowledge, this study has not been repeated.

3.2 Natriuretic Peptide Receptor-B

Natriuretic peptide receptor-B (NPR-B) is the principal receptor of C-type natriuretic peptide (CNP) and exhibits similar topology, glycosylation, and intramolecular disulfide bonding patterns as NPR-A. The extracellular and intracellular regions of rat NPR-B are 43 and 78% identical to rat NPR-A at the amino acid level, respectively (Schulz et al. 1989). NPR-B binds natriuretic peptides with a selectivity preference of CNP $\gg$ ANP $\geqslant$ BNP (Bennett et al. 1991; Koller et al. 1991; Suga et al. 1992a). The human NPR-B gene is

located on chromosome 9p12–21 and the murine version, *Npr2*, is located on chromosome 4 (Lowe et al. 1990).

Four serine and one threonine phosphorylation sites have been identified within the amino-terminal portion of NPR-B's kinase homology domain (Potter and Hunter 1998a), and receptor dephosphorylation has been shown to mediate desensitization in response to prolonged CNP exposure, protein kinase C activation, and intracellular calcium elevations (Potter 1998; Potter and Hunter 2000; Potthast et al. 2004). ATP increases the guanylyl cyclase activity of NPR-B, by decreasing its Michaelis constant (Antos and Potter 2007).

NPR-B and/or its mRNA is expressed in bone, brain, fibroblasts, heart, kidney, liver, lung, uterine, and vascular smooth muscle tissue (Bryan et al. 2006; Chrisman et al. 1993; Dickey et al. 2007; Herman et al. 1996; Langub et al. 1995). Mice with a targeted disruption of the NPR-B gene, display dwarfism and female sterility (Tamura et al. 2004). The achondroplastic (cn/cn) mouse has a spontaneous mutation in NPR-B resulting in the substitution of a highly conserved Leu with Arg in the guanylyl cyclase domain, which inactivates the enzyme. Endochondral ossification is disrupted in mice with two defective alleles, leading to dwarfism (Tsuji and Kunieda 2005). However, these mice exhibit no fertility defect. NPR-B dominant negative mutant transgenic rats have also been generated (Langenickel et al. 2006). In addition to mild growth retardation of the long bones, the rats displayed progressive, blood pressure-independent cardiac hypertrophy and an elevated heart rate. Consistent with a prominent role for CNP in the heart, NPR-B, not NPR-A, is the most active natriuretic peptide receptor in the failed heart (Dickey et al. 2007). Homologous loss-of-function mutations in human NPR-B result in a rare form of dwarfism called acromesomelic dysplasia, type Maroteaux (AMDM) (Bartels et al. 2004). Individuals with single defect NPR-B alleles are statistically shorter than the average person (Olney et al. 2006).

3.3 Natriuretic Peptide Receptor-C

Natriuretic peptide receptor-C (NPR-C) consists of a large extracellular ligand-binding domain that is approximately 30–35% identical to NPR-A and NPR-B, a single membrane-spanning region, but only 37 intracellular amino acids (Chang et al. 1989; Fuller et al. 1988; Porter et al. 1990). Unlike NPR-A and NPR-B, it contains one or two juxtamembrane intermolecular disulfide bonds. Hence, it is a disulfide-linked dimer. It has no known enzymatic activity but has been suggested to signal in a G protein-dependent manner (Rose and Giles 2008). It contains three known N-linked extracellular glycosylation sites (Stults et al. 1994) and binds natriuretic peptides with a stoichiometry of two molecules of receptor to one molecule of ligand (Ammarguellat et al. 2001). Its ligand selectivity preference is: ANP > CNP $\geqslant$ BNP (Bennett et al. 1991; Suga et al. 1992a). Compared to NPR-A and NPR-B, NPR-C has much less stringent specificity for structural variants of ANP and will bind with high affinity to ring-deleted ANP analogs (Maack et al. 1987). The main function of NPR-C, also known as the clearance receptor, is to clear circulating natriuretic peptides through the process of receptor-mediated internalization and degradation (Koh et al. 1992; Nussenzveig et al. 1990). Internalization of NPR-C occurs in the absence of ligand; thus, this is a constitutive process (Nussenzveig et al. 1990). Osteocrin, an endogenous protein with

limited homology to members of the natriuretic peptide family, binds NPR-C, but not NPR-A or NPR-B (Moffatt et al. 2007). Osteocrin is thought to compete with CNP for binding to NPR-C in bone, and therefore, increase local CNP levels during critical periods for bone development (Moffatt et al. 2007). The human NPR-C gene is located on chromosome 5p13–14 and contains 8 exons and 7 introns spanning more than 65 kilobases (Lowe et al. 1990; Rahmutula et al. 2002). *Npr3*, the murine version of the NPR-C gene, is located on chromosome 15. A splice variant of NPR-C containing an additional cysteine residue has also been identified and characterized from bovine lung (Mizuno et al. 1993).

NPR-C is the most widely and abundantly expressed natriuretic peptide receptor; for example, it constitutes ~94% of the total ANP binding sites in endothelial cells (Leitman et al. 1986). NPR-C and/or its mRNA is expressed in adrenal, brain, heart, kidney, mesentery, and vascular smooth muscle tissue (Nagase et al. 1997; Porter et al. 1990; Suga et al. 1992c; Wilcox et al. 1991). NPR-C knockout mice exhibit increased ANP half-lives, long bone overgrowth, hypotension, mild diuresis, dilute urine, and blood volume depletion (Matsukawa et al. 1999). Mouse strains containing chemically induced loss-of-function mutations in the extracellular domain of NPR-C display skeletal overgrowth from endochondral ossification defects as well (Jaubert et al. 1999).

4 Physiologic Effects of Natriuretic Peptides

Natriuretic peptides and their receptors mediate a diverse array of physiologic effects ranging from blood pressure control to endochondral ossification. This broad assortment of responses is achieved from the distinct actions of individual natriuretic peptides interacting with specific guanylyl cyclase receptors. This is particularly apparent in mice with targeted deletions of individual natriuretic peptides or natriuretic peptide receptors. The following section will highlight work describing the effects of natriuretic peptides on the cardiovascular system and bone growth.

4.1 Natriuretic Peptide Effects on Blood Pressure

ANP binding to NPR-A is a key-signaling pathway, which regulates normal homeostatic blood pressure. This is clearly demonstrated in mice lacking ANP or its receptor NPR-A, which have blood pressures that are elevated 20–40mm mercury, compared to control mice (John et al. 1995; John et al. 1996; Lopez et al. 1995; Oliver et al. 1997). The link between NPR-A and blood pressure in mice is particularly strong because Smithies and colleagues demonstrated that NPR-A copy number is inversely related to blood pressure in a remarkably linear manner (Oliver et al. 1998). Conversely, blood pressures in transgenic mice overexpressing ANP or BNP are substantially decreased (Ogawa et al. 1994a; Steinhelper et al. 1990). Although infusion of supraphysiological levels of CNP into animals acutely decreases blood pressure (Clavell et al. 1993; Sudoh et al. 1990), mice lacking functional CNP or NPR-B are normotensive (Chusho et al. 2001; Tamura et al. 2004), suggesting that the CNP/NPR-B pathway is not a fundamental regulator of basal blood pressure in mice.

NPR-A dependent decreases in blood pressure are achieved through natriuresis and diuresis, vasorelaxation, increased endothelium permeability, and antagonism of the renin-angiotensin

system. Classic experiments showed that atrial extract infusions resulted in rapid renal excretion of water and sodium (de Bold et al. 1981). Studies by Garbers and colleagues indicated that the renal response requires NPR-A because mice lacking this receptor do not respond to ANP, BNP, or to acute volume expansion (Kishimoto et al. 1996). Similar studies found that NPR-A was also required for ANP- or BNP-dependent vasorelaxation in mice (Lopez et al. 1997). Physiological experiments involving mice with severe reductions of NPR-A in vascular smooth muscle cells demonstrated that while smooth muscle NPR-A is required for acute ANP- or BNP-dependent vasorelaxation, this response does not play a significant role in controlling chronic blood pressure (Holtwick et al. 2002).

The ability of the ANP/NPR-A pathway to increase endothelial permeability is supported by the observation that hematocrit levels are elevated prior to urination and are preserved in nephrectomized animals (Almeida et al. 1986; Fluckiger et al. 1986; Richards et al. 1988). Furthermore, mice with genetically engineered reductions of NPR-A in vascular endothelium exhibit volume expansion, hypertension, and reduced albumin clearance from the vascular system (Sabrane et al. 2005).

4.2 Effects of Natriuretic Peptides on Cardiac Hypertrophy and Fibrosis

In addition to regulating blood pressure, natriuretic peptides inhibit cardiac hypertrophy and remodeling. Hypertrophy is regulated by ANP and NPR-A, whereas remodeling is regulated by both the ANP/BNP/NPR-A and the CNP/NPR-B pathways.

Although prolonged hypertension can cause hypertrophy, the level of hypertrophy in NPR-A deficient mice is significantly greater than that observed in other genetic models that cause similar levels of hypertension, suggesting that NPR-A elicits a local growth inhibitory signal in the heart. Data for this idea was initially shown in NPR-A knockout mice, which have enlarged hearts even when effectively treated with antihypertensive drugs from birth (Knowles et al. 2001). Additional studies determined that transgenic reexpression of NPR-A in the hearts of NPR-$A^{-/-}$ mice reduced cardiomyocyte size without affecting heart rate or blood pressure (Kishimoto et al. 2001). Finally, mice with reduced cardiomyocyte expression of NPR-A exhibited moderate hypertrophy even though they were slightly hypotensive (Holtwick et al. 2003; Patel et al. 2005). In terms of natriuretic peptides, mice lacking ANP have larger hearts, whereas mice transgenically overexpressing ANP have smaller hearts (Barbee et al. 1994; Steinhelper et al. 1990). In contrast, targeted deletion of BNP resulted in normotensive mice with normal heart size but with increased ventricular fibrosis – especially when subjected to pressure overload (Tamura et al. 2000). Thus, genetic studies in mice strongly support a role for ANP activation of NPR-A in the local inhibition of cardiac hypertrophy and BNP activation of NPR-A in the inhibition of cardiac fibrosis.

Recently, data supporting a role for the CNP/NPR-B pathway in cardiac remodeling has been reported. Although NPR-B inactivation mutations in mice have not been shown to cause hypertrophy (Tamura et al. 2004; Tsuji and Kunieda 2005), transgenic rats expressing a dominant negative form of NPR-B exhibit mild blood pressure-independent cardiac hypertrophy and increased heart rate (Langenickel et al. 2006). In addition, CNP infusion was shown to reduce cardiac remodeling in response to experimentally induced myocardial

infarction in rats, and transgenic expression of CNP improved outcomes in mice subjected to ischemia/reperfusion injury or myocardial infarction (Wang et al. 2007).

4.3 Effects of CNP and NPR-B on Bone Growth

The most obvious function of the CNP/NPR-B pathway is to stimulate long bone growth. Though undetectable at birth, mice lacking functional CNP or NPR-B develop dwarfism due to impaired endochondrial ossification (Chusho et al. 2001; Tamura et al. 2001; Tsuji and Kunieda 2005). Conversely, transgenic CNP overexpression or reduced degradation of CNP due to loss of function mutations in NPR-C result in skeletal overgrowth (Jaubert et al. 1999; Matsukawa et al. 1999; Yasoda et al. 2004). Growth plate histology reveals that the endochondral proliferative and hypertrophic zones are reduced in mice with impaired CNP or NPR-B signaling, whereas overexpressing mice have enlarged growth plates (Chusho et al. 2001; Tamura et al. 2004; Yasoda et al. 2004). One cGMP effector involved in the long bone growth pathway is cGMP-dependent protein kinase II, also known as PKGII or cGKII. Loss of function mutations in the mouse or rat gene that encodes this kinase also cause dwarfism (Chikuda et al. 2004; Pfeifer et al. 1996). Interestingly, the growth plates of rodents with defective cGKII are enlarged, which differs from the diminished growth plates seen in the CNP or NPR-B deleted mice, suggesting that a cGKII-independent pathway is also involved in CNP-dependent long bone growth.

Humans with two loss of function alleles for NPR-B suffer from a rare type of autosomal recessive dwarfism, called acromesomelic dysplasia, type Maroteaux (Bartels et al. 2004). These individuals are characterized by disproportionate limb to torso ratios that are only obvious a year or more after birth. Interestingly, although single copy carriers of a nonfunctional NPR-B allele do not suffer from disease, they are statistically shorter than comparable individuals with two wild type NPR-B alleles (Olney et al. 2006). Thus, it is possible that NPR-B mutations could have a significant effect on the stature of the general population.

5 Therapeutics of Natriuretic Peptides

The Encyclopedia Britannica defines therapeutics as “the treatment and care of a patient for the purpose of both preventing and combating disease”. By these criteria, natriuretic peptides have already found their way into the clinical arsenal – especially ANP and BNP. Measurement of serum BNP levels is used in the clinic as a diagnostic indicator for heart failure, and synthetic forms of both of these peptides have been approved in some countries for the treatment of heart failure (Gardner 2003). The extent of their usefulness, however, has come under question due to their limited renal actions, and trials are underway to determine the most effective use of these peptides. In this section, we will explore the history of both synthetic ANP and BNP as therapeutic agents.

5.1 Synthetic ANP (Anaritide and Carperitide)

As previously discussed, the natriuretic peptide field emerged with the key discovery that specific peptides present in atrial extracts cause natriuresis and diuresis. Initially, numerous peptide variants were identified in rat atrial extracts, but subsequent studies revealed that the

mature form of ANP is 28-amino acids and that smaller versions are degradation products that maintain various levels of activity. The most widely studied of these is the 25-amino acid peptide lacking the first three amino-terminal residues. This peptide is referred to as ANF IV and its synthetic form is called anaritide.

Since the activities of the 25-amino acid and mature 28-amino acid peptide were similar, many studies were conducted with the smaller peptide. Studies by Cody and colleagues indicated that infusion of anaritide in healthy male volunteers resulted in natriuresis, diuresis, and reduction in systolic blood pressure; however, in seven patients with congestive heart failure, the changes in urine volume and sodium excretion were minimal (Cody et al. 1986). Saito and colleagues observed a similar lack of diuresis and natriuresis, when congestive heart failed patients were infused with the mature form of ANP (Saito et al. 1987). Meanwhile, others acknowledged the renal hyporesponsiveness to anaritide in congestive heart failed patients, but indicated that the renal parameters did show a statistically significant increase in larger patient samples (Fifer et al. 1990). In Japan, clinical studies on the effectiveness of mature ANP continued; and in 1995, synthetic full length ANP (carperitide) was approved for the treatment of acute decompensated heart failure. In the United States, clinical use of BNP, not ANP, was explored for the treatment of heart failure due to its larger renal responsiveness, and possibly due to unique patient opportunities.

Investigations were also initiated to study the effectiveness of ANP in the treatment of human renal disease. Specifically, trials were conducted to evaluate the ability of anaritide infusion to reduce the need for dialysis in patients with acute tubular necrosis. The initial study with 53 patients suggested a positive outcome for patients receiving anaritide because they had increased creatinine clearance and a decreased need for dialysis (Rahman et al. 1994). This led to the formation of a multicenter placebo-controlled clinical trial in 504 patients with acute tubular necrosis. While 24-h infusion of anaritide did not improve the overall survival of the patients without dialysis, it appeared that a subset of patients might have benefited (Allgren et al. 1997). Thus, a second trial was conducted in patients with oliguric acute renal failure (renal failure resulting in the production of less than 400 ml of urine per 24 h). However, this 222 patient trial indicated no statistically significant benefit of anaritide in dialysis-free survival (Lewis et al. 2000). Both trials remarked on the severe hypotension that often occurred as a result of the anaritide infusion. In fact, it is this severe hypotension that appears to be limiting the utility of anaritide or nesiritide (see Sect. 5.2) as a therapy for either heart failure or renal disease. The authors stated in their discussion, “it is possible that if this hypotension could have been avoided, anaritide would have been efficacious” (Lewis et al. 2000).

Anaritide was also investigated for its ability to prevent radiocontrast-induced nephropathy. This form of nephropathy is a common cause of acute renal failure in the hospital setting and is defined as acute renal failure – or more specifically, an increase in blood urea nitrogen of 50% or 20 mg/dL or an increase in serum creatinine levels of 1 mg/dL within 24 h or both - occurring within 48 h of exposure to intravascular radiographic material that is not attributable to other causes (Barrett and Parfrey 1994). However, in a 247 person clinical

trial anaritide along with hydration was no more effective at preventing radiocontrast-induced nephropathy than hydration alone (Kurnik et al. 1998).

Finally, in 2004, studies conducted in Sweden compared the ability of the loop diuretic, furosemide, or mature ANP (1–28) to increase GFR, renal blood flow, and reduce renal oxygen consumption in patients with acute renal failure. However, they concluded that furosemide was a more effective agent (Sward et al. 2005). Therefore, despite its potent natriuretic and diuretic effects in normal, healthy subjects, clinical studies conducted to date indicate little or no therapeutic benefit of ANP analogs in the successful treatment of renal disease.

5.2 Synthetic BNP (Nesiritide)

Given the natriuretic effects of ANP, the related peptide BNP, was assumed to elicit a similar response. McGregor and colleagues demonstrated that administration of porcine BNP resulted in a natriuretic response and an increase in urinary excretion of cGMP (McGregor et al. 1990). Yoshimura and colleagues reported the same response in healthy volunteers to infusion of human BNP (Yoshimura et al. 1991). Furthermore, patients with congestive heart failure also responded to infusion of BNP.

The effectiveness of 24-h infusion of nesiritide to patients with congestive heart failure was examined in a multicenter, placebo-controlled trial. The peptide resulted in a reduction of both preload and afterload resulting in an increase in stroke volume and cardiac output (Mills et al. 1999). The results of a second multicenter trial, called the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) study, compared the effects of the addition of nitroglycerin or nesiritide versus placebo to standard therapy. The group treated with nesiritide had improved dyspnea after 3 h treatment, while there was no difference in the other groups. The nitroglycerin group reported more adverse effects than the nesiritide group. Additionally, patients receiving nesiritide had less adverse cardiovascular effects at either the 0.015 or 0.03μg/kg/min infusion rate compared to patients receiving dobutamine as determined by the 246-patient PRECEDENT Trial (de Lissovoy et al. 2003).

The results of these studies likely led to the approval of nesiritide, marketed under the trade name Natrecor, for the treatment of acute decompensated heart failure in the United States in 2001. In 2003, nesiritide became commercially available in Israel and Switzerland, under the trade name Noratak. However, approval in the rest of Europe was delayed pending further investigations into the renal responses of nesiritide infusion – a request that in retrospect is prophetic.

With the approval of the first new intravenous compound for the treatment of heart failure in many years, use of nesiritide was immediate. After approval, the number of patients treated with nesiritide was larger than any clinical trial and with the larger sample population came some unpleasant findings. Initially, Wang and colleagues reported in 2004 that nesiritide does not improve renal function in patients with chronic heart failure (Wang et al. 2004), but more damaging were two meta-analysis studies by Sackner-Bernstein and colleagues indicating that nesiritide worsened renal function and increased the likelihood of death (Sackner-Bernstein et al. 2005a, b).

The results of a 75-person study (BNP-CARDS study), however, suggest nesiritide has no detrimental effect on renal function, when cohorts of similar baseline renal function were compared (Witteles et al. 2007). The number of persons in this study was small, however, so a more definitive conclusion on whether nesiritide impairs renal function will have to wait until the result of more detailed, larger studies are released. Several such studies are currently in progress. One is a clinical trial enlisting at least 1,900 patients throughout Europe and Latin America – the ETNA (Evaluating Treatment with Nesiritide in Acute Decompensated Heart Failure) trial. This trial was scheduled to begin in 2006 to study the efficacy of nesiritide on treatment of acutely decompensated heart failure. Results from the trial are not yet available. The second study involving about 900 patients, called FUSION II, was conducted to determine the safety and efficacy of outpatient administration of nesiritide to patients with heart failure. Preliminary analysis indicates that nesiritide did not induce renal complications or increase patient mortality (Cleland et al. 2007). Finally, there is the ASCEND HF trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure). This trial is scheduled to compare the effects of nesiritide treatment versus placebo for a minimum of 24 h up to a maximum of 7 days in 7,000 heart failure patients.

Meanwhile, other therapeutic applications of nesiritide have also been investigated. Given that nesiritide was often reported to decrease pulmonary capillary wedge pressure, Michaels and colleagues tested its effectiveness in pulmonary hypertension (Michaels et al. 2005). However, they found no effect of a 30 min infusion. Chen and colleagues have investigated the effectiveness of subcutaneous injections of nesiritide. Their most recent paper on effects in a dog heart failure pacing model suggest that subcutaneous injection of nesiritide reduces both preload and afterload but has no effect on cardiac output (Chen et al. 2006).

5.3 Clinical Conclusions

Expectations were high when the natriuretic peptides were first approved for the treatment of acute decompensated heart failure. However, their effectiveness is clearly connected to the clinical situations in which they are used. As described above, current trials are underway to more effectively define these settings. Some of the limitations were foretold in previous studies. For example, in 1990 Fried and colleagues concluded that anaritide-induced decreases in mean arterial pressure may “limit its therapeutic potential” (Fried et al. 1990). Concerns were voiced again in 2000, when Lewis and colleagues concluded that anaritide “may be beneficial if the hypotension could be avoided” (Lewis et al. 2000). Some of these limitations of anaritide may also be true of nesiritide, even though it has higher reported renal responses in congestive heart failed patients. Nonetheless, despite current reservations about nesiritide, it is likely that it or new and improved forms will find clinical usefulness once dosage and other clinical parameters regarding efficacy and safety are optimized. For example, CD-NP, a chimeric designer peptide consisting of the carboxyl tail from Dendroaspis natriuretic peptide fused to full length CNP, retains the beneficial renal effects of BNP while being substantially less hypotensive (Lisy et al. 2008). Interestingly, the unique properties of CD-NP result, at least in part, from its ability to activate both NPR-A and NPR-B (Dickey et al, submitted). Hence, CD-NP is the first dual natriuretic peptide receptor activator.

References

Allgren RL, Marbury TC, Rahman SN, Weisberg LS, Fenves AZ, Lafayette RA, Sweet RM, Genter FC, Kurnik BR, Conger JD, Sayegh MH. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. N Engl J Med. 1997; 336:828–834. [PubMed: 9062091]

Almeida FA, Suzuki M, Maack T. Atrial natriuretic factor increases hematocrit and decreases plasma volume in nephrectomized rats. Life Sci. 1986; 39:1193–1199. [PubMed: 2943959]

Ammarguellat F, Larouche I, Schiffrin EL. Myocardial fibrosis in DOCA-salt hypertensive rats: effect of endothelin ET(A) receptor antagonism. Circulation. 2001; 103:319–324. [PubMed: 11208696]

Antos LK, Abbey-Hosch SE, Flora DR, Potter LR. ATP-independent activation of natriuretic peptide receptors. J Biol Chem. 2005; 280:26928–26932. [PubMed: 15911610]

Antos LK, Potter LR. Adenine nucleotides decrease the apparent Km of endogenous natriuretic peptide receptors for GTP. Am J Physiol Endocrinol Metab. 2007; 293:E1756–1763. [PubMed: 17848634]

Barbee RW, Perry BD, Re RN, Murgo JP, Field LJ. Hemodynamics in transgenic mice with overexpression of atrial natriuretic factor. Circ Res. 1994; 74:747–751. [PubMed: 8137510]

Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents. N Engl J Med. 1994; 331:1449–1450. [PubMed: 7969286]

Bartels CF, Bukulmez H, Padayatti P, Rhee DK, van Ravenswaaij-Arts C, Pauli RM, Mundlos S, Chitayat D, Shih LY, Al-Gazali LI, Kant S, Cole T, Morton J, Cormier-Daire V, Faivre L, Lees M, Kirk J, Mortier GR, Leroy J, Zabel B, Kim CA, Crow Y, Braverman NE, van den Akker F, Warman MLA. Mutations in the transmembrane natriuretic peptide receptor NPR-B impair skeletal growth and cause acromesomelic dysplasia, type Maroteaux. Am J Hum Genet. 2004; 75:27–34. [PubMed: 15146390]

Bennett BD, Bennett GL, Vitangcol RV, Jewett JR, Burnier J, Henzel W, Lowe DG. Extracellular domain-IgG fusion proteins for three human natriuretic peptide receptors. Hormone pharmacology and application to solid phase screening of synthetic peptide antisera. J Biol Chem. 1991; 266:23060–23067. [PubMed: 1660465]

Bilder GE, Schofield TL, Blaine EH. Release of atrial natriuretic factor. Effects of repetitive stretch and temperature. Am J Physiol. 1986; 251:F817–F821. [PubMed: 2946240]

Bocciardi R, Giorda R, Buttgereit J, Gimelli S, Divizia MT, Beri S, Garofalo S, Tavella S, Lerone M, Zuffardi O, Bader M, Ravazzolo R, Gimelli G. Overexpression of the C-type natriuretic peptide (CNP) is associated with overgrowth and bone anomalies in an individual with balanced t(2;7) translocation. Hum Mutat. 2007; 28:724–731. [PubMed: 17373680]

Brown J, Chen Q, Hong G. An autocrine system for C-type natriuretic peptide within rat carotid neointima during arterial repair. Am J Physiol. 1997; 272:H2919–H2931. [PubMed: 9227572]

Bryan PM, Smirnov D, Smolenski A, Feil S, Feil R, Hofmann F, Lohmann S, Potter LR. A Sensitive Method for Determining the Phosphorylation Status of Natriuretic Peptide Receptors: cGK-Ialpha Does Not Regulate NPR-A. Biochemistry. 2006; 45:1295–1303. [PubMed: 16430226]

Burczynska B, Duda T, Sharma RK. ATP signaling site in the ARM domain of atrial natriuretic factor receptor guanylate cyclase. Mol Cell Biochem. 2007; 301:93–107. [PubMed: 17277921]

Burnett JC Jr, Kao PC, Hu DC, Heser DW, Heublein D, Granger JP, Opgenorth TJ, Reeder GS. Atrial natriuretic peptide elevation in congestive heart failure in the human. Science. 1986; 231:1145–1147. [PubMed: 2935937]

Chan JC, Knudson O, Wu F, Morser J, Dole WP, Wu Q. Hypertension in mice lacking the proatrial natriuretic peptide convertase corin. Proc Natl Acad Sci U S A. 2005; 102:785–790. [PubMed: 15637153]

Chang MS, Lowe DG, Lewis M, Hellmiss R, Chen E, Goeddel DV. Differential activation by atrial and brain natriuretic peptides of two different receptor guanylate cyclases. Nature. 1989; 341:68–72. [PubMed: 2570358]

Charles CJ, Prickett TC, Espiner EA, Rademaker MT, Richards AM, Yandle TG. Regional sampling and the effects of experimental heart failure in sheep: differential responses in A, B and C-type natriuretic peptides. Peptides. 2006; 27:62–68. [PubMed: 16095755]

Chen HH, Schirger JA, Cataliotti A, Burnett JC Jr. Intact acute cardiorenal and humoral responsiveness following chronic subcutaneous administration of the cardiac peptide BNP in experimental heart failure. Eur J Heart Fail. 2006; 8:681–686. [PubMed: 16459135]

Chikuda H, Kugimiya F, Hoshi K, Ikeda T, Ogasawara T, Shimoaka T, Kawano H, Kamekura S, Tsuchida A, Yokoi N, Nakamura K, Komeda K, Chung UI, Kawaguchi H. Cyclic GMP-dependent protein kinase II is a molecular switch from proliferation to hypertrophic differentiation of chondrocytes. Genes Dev. 2004; 18:2418–2429. [PubMed: 15466490]

Chinkers M, Wilson EM. Ligand-independent oligomerization of natriuretic peptide receptors. Identification of heteromeric receptors and a dominant negative mutant. J Biol Chem. 1992; 267:18589–18597. [PubMed: 1382057]

Chrisman TD, Schulz S, Potter LR, Garbers DL. Seminal plasma factors that cause large elevations in cellular cyclic GMP are C-type natriuretic peptides. J Biol Chem. 1993; 268:3698–3703. [PubMed: 8094083]

Chun TH, Itoh H, Ogawa Y, Tamura N, Takaya K, Igaki T, Yamashita J, Doi K, Inoue M, Masatsugu K, Korenaga R, Ando J, Nakao K. Shear stress augments expression of C-type natriuretic peptide and adrenomedullin. Hypertension. 1997; 29:1296–1302. [PubMed: 9180632]

Chusho H, Tamura N, Ogawa Y, Yasoda A, Suda M, Miyazawa T, Nakamura K, Nakao K, Kurihara T, Komatsu Y, Itoh H, Tanaka K, Saito Y, Katsuki M. Dwarfism and early death in mice lacking C-type natriuretic peptide. Proc Natl Acad Sci U S A. 2001; 98:4016–4021. [PubMed: 11259675]

Clavell AL, Stingo AJ, Wei CM, Heublein DM, Burnett JC Jr. C-type natriuretic peptide: a selective cardiovascular peptide. Am J Physiol. 1993; 264:R290–295. [PubMed: 8383462]

Cleland JG, Coletta AP, Clark AL. Clinical trials update from the American College of Cardiology 2007: ALPHA, EVEREST, FUSION II, VALIDD, PARR-2, REMODEL, SPICE, COURAGE, COACH, REMADHE, pro-BNP for the evaluation of dyspnoea and THIS-diet. Eur J Heart Fail. 2007; 9:740–745. [PubMed: 17481946]

Cody RJ, Atlas SA, Laragh JH, Kubo SH, Covit AB, Ryman KS, Shaknovich A, Pondolfino K, Clark M, Camargo MJ, Scarborough RM, Lewicki JA. Atrial natriuretic factor in normal subjects and heart failure patients. Plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. J Clin Invest. 1986; 78:1362–1374. [PubMed: 2945832]

Currie MG, Geller DM, Cole BR, Siegel NR, Fok KF, Adams SP, Eubanks SR, Galluppi GR, Needleman P. Purification and sequence analysis of bioactive atrial peptides (atriopeptins). Science. 1984; 223:67–69. [PubMed: 6419347]

de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci. 1981; 28:89–94. [PubMed: 7219045]

de Lissovoy G, Stier DM, Ciesla G, Munger M, Burger AJ. Economic implications of nesiritide versus dobutamine in the treatment of patients with acutely decompensated congestive heart failure. Am J Cardiol. 2003; 92:631–633. [PubMed: 12943895]

Del Ry S, Passino C, Maltinti M, Emdin M, Giannessi D. C-type natriuretic peptide plasma levels increase in patients with chronic heart failure as a function of clinical severity. Eur J Heart Fail. 2005; 7:1145–1148. [PubMed: 15922659]

Dickey DM, Flora DR, Bryan PM, Xu X, Chen Y, Potter LR. Differential regulation of membrane guanylyl cyclases in congestive heart failure: natriuretic peptide receptor (NPR)-B, Not NPR-A, is the predominant natriuretic peptide receptor in the failing heart. Endocrinology. 2007; 148:3518–3522. [PubMed: 17412809]

Edwards BS, Zimmerman RS, Schwab TR, Heublein DM, Burnett JC Jr. Atrial stretch, not pressure, is the principal determinant controlling the acute release of atrial natriuretic factor. Circ Res. 1988; 62:191–195. [PubMed: 2962782]

Fan D, Bryan PM, Antos LK, Potthast RJ, Potter LR. Down-Regulation Does Not Mediate Natriuretic Peptide-Dependent Desensitization of Natriuretic Peptide Receptor (NPR)-A or NPR-B: Guanylyl Cyclase-Linked Natriuretic Peptide Receptors Do Not Internalize. Mol Pharmacol. 2005; 67:174–183. [PubMed: 15459247]

Fifer MA, Molina CR, Quiroz AC, Giles TD, Herrmann HC, De Scheerder IR, Clement DL, Kubo S, Cody RJ, Cohn JN, et al. Hemodynamic and renal effects of atrial natriuretic peptide in congestive heart failure. Am J Cardiol. 1990; 65:211–216. [PubMed: 2136969]

Fluckiger JP, Waeber B, Matsueda G, Delaloye B, Nussberger J, Brunner HR. Effect of atriopeptin III on hematocrit and volemia of nephrectomized rats. Am J Physiol. 1986; 251:H880–H883. [PubMed: 2945444]

Flynn TG, de Bold ML, de Bold AJ. The amino acid sequence of an atrial peptide with potent diuretic and natriuretic properties. Biochem Biophys Res Commun. 1983; 117:859–865. [PubMed: 6230081]

Forssmann WG, Richter R, Meyer M. The endocrine heart and natriuretic peptides: histochemistry, cell biology, and functional aspects of the renal urodilatin system. Histochem Cell Biol. 1998; 110:335–357. [PubMed: 9792413]

Fried T, Aronoff GR, Benabe JE, Brunner HR, DiBona GF, Fleischhauer T, Lam M, Lawton WJ, Luft FC, Martinez-Maldonado M, et al. Renal and hemodynamic effects of atrial natriuretic peptide in patients with cirrhosis. Am J Med Sci. 1990; 299:2–9. [PubMed: 2136974]

Fuller F, Porter JG, Arfsten AE, Miller J, Schilling JW, Scarborough RM, Lewicki JA, Schenk DB. Atrial natriuretic peptide clearance receptor. Complete sequence and functional expression of cDNA clones. J Biol Chem. 1988; 263:9395–9401. [PubMed: 2837487]

Gardner DG. Natriuretic peptides: markers or modulators of cardiac hypertrophy? Trends Endocrinol Metab. 2003; 14:411–416. [PubMed: 14580760]

Goy MF, Oliver PM, Purdy KE, Knowles JW, Fox JE, Mohler PJ, Qian X, Smithies O, Maeda N. Evidence for a novel natriuretic peptide receptor that prefers brain natriuretic peptide over atrial natriuretic peptide. Biochem J. 2001; 358:379–387. [PubMed: 11513736]

Grepin C, Dagnino L, Robitaille L, Haberstroh L, Antakly T, Nemer M. A hormone-encoding gene identifies a pathway for cardiac but not skeletal muscle gene transcription. Mol Cell Biol. 1994; 14:3115–3129. [PubMed: 8164667]

Henry JP, Gauer OH, Reeves JL. Evidence of the atrial location of receptors influencing urine flow. Circ Res. 1956; 4:85–90. [PubMed: 13277115]

Herman JP, Dolgas CM, Rucker D, Langub MC Jr. Localization of natriuretic peptide-activated guanylate cyclase mRNAs in the rat brain. J Comp Neurol. 1996; 369:165–187. [PubMed: 8726993]

Holtwick R, Gotthardt M, Skryabin B, Steinmetz M, Potthast R, Zetsche B, Hammer RE, Herz J, Kuhn M. Smooth muscle-selective deletion of guanylyl cyclase-A prevents the acute but not chronic effects of ANP on blood pressure. Proc Natl Acad Sci U S A. 2002; 99:7142–7147. [PubMed: 11997476]

Holtwick R, Van Eickels M, Skryabin BV, Baba HA, Bubikat A, Begrow F, Schneider MD, Garbers DL, Kuhn M. Pressure-independent cardiac hypertrophy in mice with cardiomyocyte-restricted inactivation of the atrial natriuretic peptide receptor guanylyl cyclase-A. J Clin Invest. 2003; 111:1399–1407. [PubMed: 12727932]

Hunt PJ, Richards AM, Espiner EA, Nicholls MG, Yandle TG. Bioactivity and metabolism of C-type natriuretic peptide in normal man. J Clin Endocrinol Metab. 1994; 78:1428–1435. [PubMed: 8200946]

Iwata T, Uchida-Mizuno K, Katafuchi T, Ito T, Hagiwara H, Hirose S. Bifunctional atrial natriuretic peptide receptor (type A) exists as a disulfide-linked tetramer in plasma membranes of bovine adrenal cortex. J Biochem (Tokyo). 1991; 110:35–39. [PubMed: 1657900]

Jamieson JD, Palade GE. Specific Granules in Atrial Muscle Cells. J Cell Biol. 1964; 23:151–172. [PubMed: 14228508]

Jaubert J, Jaubert F, Martin N, Washburn LL, Lee BK, Eicher EM, Guenet JL. Three new allelic mouse mutations that cause skeletal overgrowth involve the natriuretic peptide receptor C gene (Npr3). Proc Natl Acad Sci U S A. 1999; 96:10278–10283. [PubMed: 10468599]

Jiao Y, Yan J, Jiao F, Yang H, Donahue LR, Li X, Roe BA, Stuart J, Gu W. A single nucleotide mutation in Nppc is associated with a long bone abnormality in lbab mice. BMC Genet. 2007; 8:16. [PubMed: 17439653]

John SW, Krege JH, Oliver PM, Hagaman JR, Hodgin JB, Pang SC, Flynn TG, Smithies O. Genetic decreases in atrial natriuretic peptide and salt-sensitive hypertension [published erratum appears in Science 1995 Mar 24;267(5205):1753]. Science. 1995; 267:679–681. [PubMed: 7839143]

John SW, Veress AT, Honrath U, Chong CK, Peng L, Smithies O, Sonnenberg H. Blood pressure and fluid-electrolyte balance in mice with reduced or absent ANP. Am J Physiol. 1996; 271:R109–114. [PubMed: 8760210]

Joubert S, Jossart C, McNicoll N, De Lean A. Atrial natriuretic peptide-dependent photolabeling of a regulatory ATP-binding site on the natriuretic peptide receptor-A. FEBS J. 2005; 272:5572–5583. [PubMed: 16262696]

Kalra PR, Clague JR, Bolger AP, Anker SD, Poole-Wilson PA, Struthers AD, Coats AJ. Myocardial production of C-type natriuretic peptide in chronic heart failure. Circulation. 2003; 107:571–573. [PubMed: 12566368]

Kangawa K, Tawaragi Y, Oikawa S, Mizuno A, Sakuragawa Y, Nakazato H, Fukuda A, Minamino N, Matsuo H. Identification of rat gamma atrial natriuretic polypeptide and characterization of the cDNA encoding its precursor. Nature. 1984; 312:152–155. [PubMed: 6239103]

Kenny AJ, Bourne A, Ingram J. Hydrolysis of human and pig brain natriuretic peptides, urodilatin, C-type natriuretic peptide and some C-receptor ligands by endopeptidase-24.11. Biochem J. 1993; 291(Pt 1):83–88. [PubMed: 8097089]

Kisch B. Electron microscopy of the atrium of the heart. I. Guineo pig. Exp Med Surg. 1956; 14:99–112. [PubMed: 13365605]

Kishimoto I, Dubois SK, Garbers DL. The heart communicates with the kidney exclusively through the guanylyl cyclase-A receptor: acute handling of sodium and water in response to volume expansion. Proc Natl Acad Sci U S A. 1996; 93:6215–6219. [PubMed: 8650246]

Kishimoto I, Rossi K, Garbers DL. A genetic model provides evidence that the receptor for atrial natriuretic peptide (guanylyl cyclase-A) inhibits cardiac ventricular myocyte hypertrophy. Proc Natl Acad Sci U S A. 2001; 98:2703–2706. [PubMed: 11226303]

Knowles JW, Esposito G, Mao L, Hagaman JR, Fox JE, Smithies O, Rockman HA, Maeda N. Pressure-independent enhancement of cardiac hypertrophy in natriuretic peptide receptor A-deficient mice. J Clin Invest. 2001; 107:975–984. [PubMed: 11306601]

Koh GY, Nussenzveig DR, Okolicany J, Price DA, Maack T. Dynamics of atrial natriuretic factor-guanylate cyclase receptors and receptor-ligand complexes in cultured glomerular mesangial and renomedullary interstitial cells. J Biol Chem. 1992; 267:11987–11994. [PubMed: 1351054]

Koller KJ, Lowe DG, Bennett GL, Minamino N, Kangawa K, Matsuo H, Goeddel DV. Selective activation of the B natriuretic peptide receptor by C-type natriuretic peptide (CNP). Science. 1991; 252:120–123. [PubMed: 1672777]

Kuhn M, Holtwick R, Baba HA, Perriard JC, Schmitz W, Ehler E. Progressive cardiac hypertrophy and dysfunction in atrial natriuretic peptide receptor (GC-A) deficient mice. Heart. 2002; 87:368–374. [PubMed: 11907014]

Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis. 1998; 31:674–680. [PubMed: 9531185]

Labrecque J, Deschenes J, McNicoll N, De Lean A. Agonistic induction of a covalent dimer in a mutant of natriuretic peptide receptor-A documents a juxtamembrane interaction that accompanies receptor activation. J Biol Chem. 2001; 276:8064–8072. [PubMed: 11124937]

Lang RE, Tholken H, Ganten D, Luft FC, Ruskoaho H, Unger T. Atrial natriuretic factor–a circulating hormone stimulated by volume loading. Nature. 1985; 314:264–266. [PubMed: 3157062]

Langenickel TH, Buttgereit J, Pagel-Langenickel I, Lindner M, Monti J, Beuerlein K, Al-Saadi N, Plehm R, Popova E, Tank J, Dietz R, Willenbrock R, Bader M. Cardiac hypertrophy in transgenic rats expressing a dominant-negative mutant of the natriuretic peptide receptor B. Proc Natl Acad Sci U S A. 2006; 103:4735–4740. [PubMed: 16537417]

Langub MC Jr, Dolgas CM, Watson RE Jr, Herman JP. The C-type natriuretic peptide receptor is the predominant natriuretic peptide receptor mRNA expressed in rat hypothalamus. J Neuroendocrinol. 1995; 7:305–309. [PubMed: 7647773]

Leitman DC, Andresen JW, Kuno T, Kamisaki Y, Chang JK, Murad F. Identification of multiple binding sites for atrial natriuretic factor by affinity cross-linking in cultured endothelial cells. J Biol Chem. 1986; 261:11650–11655. [PubMed: 3017939]

Lewis J, Salem MM, Chertow GM, Weisberg LS, McGrew F, Marbury TC, Allgren RL. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. Am J Kidney Dis. 2000; 36:767–774. [PubMed: 11007679]

Lisy O, Huntley BK, McCormick DJ, Kurlansky PA, Burnett JC Jr. Design, synthesis, and actions of a novel chimeric natriuretic peptide: CD-NP. J Am Coll Cardiol. 2008; 52:60–68. [PubMed: 18582636]

Lopez MJ, Garbers DL, Kuhn M. The guanylyl cyclase-deficient mouse defines differential pathways of natriuretic peptide signaling. J Biol Chem. 1997; 272:23064–23068. [PubMed: 9287305]

Lopez MJ, Wong SK, Kishimoto I, Dubois S, Mach V, Friesen J, Garbers DL, Beuve A. Salt-resistant hypertension in mice lacking the guanylyl cyclase-A receptor for atrial natriuretic peptide. Nature. 1995; 378:65–68. [PubMed: 7477288]

Lowe DG, Chang MS, Hellmiss R, Chen E, Singh S, Garbers DL, Goeddel DV. Human atrial natriuretic peptide receptor defines a new paradigm for second messenger signal transduction. EMBO J. 1989; 8:1377–1384. [PubMed: 2569967]

Lowe DG, Klisak I, Sparkes RS, Mohandas T, Goeddel DV. Chromosomal distribution of three members of the human natriuretic peptide receptor/guanylyl cyclase gene family. Genomics. 1990; 8:304–312. [PubMed: 1979052]

Lu B, Gerard NP, Kolakowski LF Jr, Bozza M, Zurakowski D, Finco O, Carroll MC, Gerard C. Neutral endopeptidase modulation of septic shock. J Exp Med. 1995; 181:2271–2275. [PubMed: 7760013]

Maack T, Suzuki M, Almeida FA, Nussenzveig D, Scarborough RM, McEnroe GA, Lewicki JA. Physiological role of silent receptors of atrial natriuretic factor. Science. 1987; 238:675–678. [PubMed: 2823385]

Matsukawa N, Grzesik WJ, Takahashi N, Pandey KN, Pang S, Yamauchi M, Smithies O. The natriuretic peptide clearance receptor locally modulates the physiological effects of the natriuretic peptide system. Proc Natl Acad Sci U S A. 1999; 96:7403–7408. [PubMed: 10377427]

McGregor A, Richards M, Espiner E, Yandle T, Ikram H. Brain natriuretic peptide administered to man: actions and metabolism. J Clin Endocrinol Metab. 1990; 70:1103–1107. [PubMed: 2156886]

Michaels AD, Chatterjee K, De Marco T. Effects of intravenous nesiritide on pulmonary vascular hemodynamics in pulmonary hypertension. J Card Fail. 2005; 11:425–431. [PubMed: 16105633]

Mills RM, LeJemtel TH, Horton DP, Liang C, Lang R, Silver MA, Lui C, Chatterjee K. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. J Am Coll Cardiol. 1999; 34:155–162. [PubMed: 10400005]

Misono KS, Grammer RT, Fukumi H, Inagami T. Rat atrial natriuretic factor: isolation, structure and biological activities of four major peptides. Biochem Biophys Res Commun. 1984; 123:444–451. [PubMed: 6541480]

Miyagi M, Misono KS. Disulfide bond structure of the atrial natriuretic peptide receptor extracellular domain: conserved disulfide bonds among guanylate cyclase-coupled receptors. Biochim Biophys Acta. 2000; 1478:30–38. [PubMed: 10719172]

Miyagi M, Zhang X, Misono KS. Glycosylation sites in the atrial natriuretic peptide receptor Oligosaccharide structures are not required for hormone binding. Eur J Biochem. 2000; 267:5758–5768. [PubMed: 10971587]

Mizuno T, Iwashina M, Itakura M, Hagiwara H, Hirose S. A variant form of the type C atrial natriuretic peptide receptor generated by alternative RNA splicing. J Biol Chem. 1993; 268:5162–5167. [PubMed: 8444892]

Moffatt P, Thomas G, Sellin K, Bessette MC, Lafreniere F, Akhouayri O, St-Arnaud R, Lanctot C. Osteocrin is a specific ligand of the natriuretic Peptide clearance receptor that modulates bone growth. J Biol Chem. 2007; 282:36454–36462. [PubMed: 17951249]

Moncla A, Missirian C, Cacciagli P, Balzamo E, Legeai-Mallet L, Jouve JL, Chabrol B, Le Merrer M, Plessis G, Villard L, Philip N. A cluster of translocation breakpoints in 2q37 is associated with

overexpression of NPPC in patients with a similar overgrowth phenotype. Hum Mutat. 2007; 28:1183–1188. [PubMed: 17676597]

Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, Shirakami G, Jougasaki M, Obata K, Yasue H, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest. 1991; 87:1402–1412. [PubMed: 1849149]

Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, Shirakami G, Jougasaki M, Imura H. Increased human brain natriuretic peptide in congestive heart failure. N Engl J Med. 1990; 323:757–758. [PubMed: 2143809]

Nagase M, Katafuchi T, Hirose S, Fujita T. Tissue distribution and localization of natriuretic peptide receptor subtypes in stroke-prone spontaneously hypertensive rats. J Hypertens. 1997; 15:1235–1243. [PubMed: 9383172]

Nakao K, Sugawara A, Morii N, Sakamoto M, Yamada T, Itoh H, Shiono S, Saito Y, Nishimura K, Ban T, et al. The pharmacokinetics of alpha-human atrial natriuretic polypeptide in healthy subjects. Eur J Clin Pharmacol. 1986; 31:101–103. [PubMed: 2946587]

Nakayama T, Soma M, Takahashi Y, Rehemudula D, Kanmatsuse K, Furuya K. Functional deletion mutation of the 5″-flanking region of type A human natriuretic peptide receptor gene and its association with essential hypertension and left ventricular hypertrophy in the Japanese. Circ Res. 2000; 86:841–845. [PubMed: 10785505]

Nussenzveig DR, Lewicki JA, Maack T. Cellular mechanisms of the clearance function of type C receptors of atrial natriuretic factor. J Biol Chem. 1990; 265:20952–20958. [PubMed: 2174430]

Ogawa Y, Itoh H, Tamura N, Suga S, Yoshimasa T, Uehira M, Matsuda S, Shiono S, Nishimoto H, Nakao K. Molecular cloning of the complementary DNA and gene that encode mouse brain natriuretic peptide and generation of transgenic mice that overexpress the brain natriuretic peptide gene. J Clin Invest. 1994a; 93:1911–1921. [PubMed: 8182124]

Ogawa Y, Itoh H, Yoshitake Y, Inoue M, Yoshimasa T, Serikawa T, Nakao K. Molecular cloning and chromosomal assignment of the mouse C-type natriuretic peptide (CNP) gene (Nppc): comparison with the human CNP gene (NPPC). Genomics. 1994b; 24:383–387. [PubMed: 7698765]

Oikawa S, Imai M, Ueno A, Tanaka S, Noguchi T, Nakazato H, Kangawa K, Fukuda A, Matsuo H. Cloning and sequence analysis of cDNA encoding a precursor for human atrial natriuretic polypeptide. Nature. 1984; 309:724–726. [PubMed: 6203042]

Oliver PM, Fox JE, Kim R, Rockman HA, Kim HS, Reddick RL, Pandey KN, Milgram SL, Smithies O, Maeda N. Hypertension, cardiac hypertrophy, and sudden death in mice lacking natriuretic peptide receptor A. Proc Natl Acad Sci U S A. 1997; 94:14730–14735. [PubMed: 9405681]

Oliver PM, John SW, Purdy KE, Kim R, Maeda N, Goy MF, Smithies O. Natriuretic peptide receptor 1 expression influences blood pressures of mice in a dose-dependent manner. Proc Natl Acad Sci U S A. 1998; 95:2547–2551. [PubMed: 9482923]

Olney RC, Bukulmez H, Bartels CF, Prickett TC, Espiner EA, Potter LR, Warman ML. Heterozygous mutations in natriuretic peptide receptor-B (NPR2) are associated with short stature. J Clin Endocrinol Metab. 2006; 91:1229–1232. [PubMed: 16384845]

Pandey KN. Intracellular trafficking and metabolic turnover of ligand-bound guanylyl cyclase/atrial natriuretic peptide receptor-A into subcellular compartments. Mol Cell Biochem. 2002; 230:61–72. [PubMed: 11952097]

Pankow K, Wang Y, Gembardt F, Krause E, Sun X, Krause G, Schultheiss HP, Siems WE, Walther T. Successive action of meprin A and neprilysin catabolizes B-type natriuretic peptide. Circ Res. 2007; 101:875–882. [PubMed: 17823376]

Patel JB, Valencik ML, Pritchett AM, Burnett JC Jr, McDonald JA, Redfield MM. Cardiac-specific attenuation of natriuretic peptide A receptor activity accentuates adverse cardiac remodeling and mortality in response to pressure overload. Am J Physiol Heart Circ Physiol. 2005; 289:H777–H784. [PubMed: 15778276]

Pfeifer A, Aszodi A, Seidler U, Ruth P, Hofmann F, Fassler R. Intestinal secretory defects and dwarfism in mice lacking cGMP- dependent protein kinase II. Science. 1996; 274:2082–2086. [PubMed: 8953039]

Porter JG, Arfsten A, Fuller F, Miller JA, Gregory LC, Lewicki JA. Isolation and functional expression of the human atrial natriuretic peptide clearance receptor cDNA. Biochem Biophys Res Commun. 1990; 171:796–803. [PubMed: 2169733]

Potter LR. Phosphorylation-dependent regulation of the guanylyl cyclase-linked natriuretic peptide receptor B: dephosphorylation is a mechanism of desensitization. Biochemistry. 1998; 37:2422–2429. [PubMed: 9485390]

Potter LR, Garbers DL. Dephosphorylation of the guanylyl cyclase-A receptor causes desensitization. J Biol Chem. 1992; 267:14531–14534. [PubMed: 1353076]

Potter LR, Garbers DL. Protein kinase C-dependent desensitization of the atrial natriuretic peptide receptor is mediated by dephosphorylation. J Biol Chem. 1994; 269:14636–14642. [PubMed: 7910166]

Potter LR, Hunter T. Identification and characterization of the major phosphorylation sites of the B-type natriuretic peptide receptor. J Biol Chem. 1998a; 273:15533–15539. [PubMed: 9624142]

Potter LR, Hunter T. Phosphorylation of the kinase homology domain is essential for activation of the A-type natriuretic peptide receptor. Mol Cell Biol. 1998b; 18:2164–2172. [PubMed: 9528788]

Potter LR, Hunter T. Activation of PKC Stimulates the Dephosphorylation of Natriuretic Peptide Receptor-B at a Single Serine Residue: a Possible Mechanism of Heterologous Desensitization. J Biol Chem. 2000; 275:31099–31106. [PubMed: 10915802]

Potthast R, Abbey-Hosch SE, Antos LK, Marchant JS, Kuhn M, Potter LR. Calcium-dependent Dephosphorylation Mediates the Hyperosmotic and Lysophosphatidic Acid-dependent Inhibition of Natriuretic Peptide Receptor-B/Guanylyl Cyclase-B. J Biol Chem. 2004; 279:48513–48519. [PubMed: 15371450]

Rahman SN, Kim GE, Mathew AS, Goldberg CA, Allgren R, Schrier RW, Conger JD. Effects of atrial natriuretic peptide in clinical acute renal failure. Kidney Int. 1994; 45:1731–1738. [PubMed: 7933821]

Rahmutula D, Nakayama T, Soma M, Kosuge K, Aoi N, Izumi Y, Kanmatsuse K, Ozawa Y. Structure and polymorphisms of the human natriuretic peptide receptor C gene. Endocrine. 2002; 17:85–90. [PubMed: 12041919]

Richards AM, Tonolo G, Montorsi P, Finlayson J, Fraser R, Inglis G, Towrie A, Morton JJ. Low dose infusions of 26- and 28-amino acid human atrial natriuretic peptides in normal man. J Clin Endocrinol Metab. 1988; 66:465–472. [PubMed: 2965159]

Rose RA, Giles WR. Natriuretic peptide C receptor signalling in the heart and vasculature. J Physiol. 2008; 586:353–366. [PubMed: 18006579]

Ruskoaho H. Cardiac hormones as diagnostic tools in heart failure. Endocr Rev. 2003; 24:341–356. [PubMed: 12788803]

Sabrane K, Kruse MN, Fabritz L, Zetsche B, Mitko D, Skryabin BV, Zwiener M, Baba HA, Yanagisawa M, Kuhn M. Vascular endothelium is critically involved in the hypotensive and hypovolemic actions of atrial natriuretic peptide. J Clin Invest. 2005; 115:1666–1674. [PubMed: 15931395]

Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. Jama. 2005a; 293:1900–1905. [PubMed: 15840865]

Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation. 2005b; 111:1487–1491. [PubMed: 15781736]

Saito Y, Nakao K, Nishimura K, Sugawara A, Okumura K, Obata K, Sonoda R, Ban T, Yasue H, Imura H. Clinical application of atrial natriuretic polypeptide in patients with congestive heart failure: beneficial effects on left ventricular function. Circulation. 1987; 76:115–124. [PubMed: 2954723]

Schulz S, Singh S, Bellet RA, Singh G, Tubb DJ, Chin H, Garbers DL. The primary structure of a plasma membrane guanylate cyclase demonstrates diversity within this new receptor family. Cell. 1989; 58:1155–1162. [PubMed: 2570641]

Steinhelper ME, Cochrane KL, Field LJ. Hypotension in transgenic mice expressing atrial natriuretic factor fusion genes. Hypertension. 1990; 16:301–307. [PubMed: 2144261]

Stephenson SL, Kenny AJ. The hydrolysis of alpha-human atrial natriuretic peptide by pig kidney microvillar membranes is initiated by endopeptidase-24.11. Biochem J. 1987; 243:183–187. [PubMed: 3038078]

Stults JT, O'Connell KL, Garcia C, Wong S, Engel AM, Garbers DL, Lowe DG. The disulfide linkages and glycosylation sites of the human natriuretic peptide receptor-C homodimer. Biochemistry. 1994; 33:11372–11381. [PubMed: 7727388]

Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature. 1988; 332:78–81. [PubMed: 2964562]

Sudoh T, Minamino N, Kangawa K, Matsuo H. C-type natriuretic peptide (CNP): a new member of natriuretic peptide family identified in porcine brain. Biochem Biophys Res Commun. 1990; 168:863–870. [PubMed: 2139780]

Suga S, Itoh H, Komatsu Y, Ogawa Y, Hama N, Yoshimasa T, Nakao K. Cytokine-induced C-type natriuretic peptide (CNP) secretion from vascular endothelial cells–evidence for CNP as a novel autocrine/paracrine regulator from endothelial cells. Endocrinology. 1993; 133:3038–3041. [PubMed: 8243333]

Suga S, Nakao K, Hosoda K, Mukoyama M, Ogawa Y, Shirakami G, Arai H, Saito Y, Kambayashi Y, Inouye K, Imura H. Receptor selectivity of natriuretic peptide family, atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide. Endocrinology. 1992a; 130:229–239. [PubMed: 1309330]

Suga S, Nakao K, Itoh H, Komatsu Y, Ogawa Y, Hama N, Imura H. Endothelial production of C-type natriuretic peptide and its marked augmentation by transforming growth factor-beta. Possible existence of “vascular natriuretic peptide system”. J Clin Invest. 1992b; 90:1145–1149. [PubMed: 1522222]

Suga S, Nakao K, Kishimoto I, Hosoda K, Mukoyama M, Arai H, Shirakami G, Ogawa Y, Komatsu Y, Nakagawa O, et al. Phenotype-related alteration in expression of natriuretic peptide receptors in aortic smooth muscle cells. Circ Res. 1992c; 71:34–39. [PubMed: 1318796]

Sward K, Valsson F, Sellgren J, Ricksten SE. Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. Intensive Care Med. 2005; 31:79–85. [PubMed: 15565364]

Takahashi Y, Nakayama T, Soma M, Izumi Y, Kanmatsuse K. Organization of the human natriuretic peptide receptor A gene. Biochem Biophys Res Commun. 1998; 246:736–739. [PubMed: 9618281]

Tamura N, Chrisman TD, Garbers DL. The regulation and physiological roles of the guanylyl cyclase receptors. Endocr J. 2001; 48:611–634. [PubMed: 11873860]

Tamura N, Doolittle LK, Hammer RE, Shelton JM, Richardson JA, Garbers DL. Critical roles of the guanylyl cyclase B receptor in endochondral ossification and development of female reproductive organs. Proc Natl Acad Sci U S A. 2004; 101:17300–17305. [PubMed: 15572448]

Tamura N, Ogawa Y, Chusho H, Nakamura K, Nakao K, Suda M, Kasahara M, Hashimoto R, Katsuura G, Mukoyama M, Itoh H, Saito Y, Tanaka I, Otani H, Katsuki M. Cardiac fibrosis in mice lacking brain natriuretic peptide. Proc Natl Acad Sci U S A. 2000; 97:4239–4244. [PubMed: 10737768]

Tawaragi Y, Fuchimura K, Tanaka S, Minamino N, Kangawa K, Matsuo H. Gene and precursor structures of human C-type natriuretic peptide. Biochem Biophys Res Commun. 1991; 175:645–651. [PubMed: 2018508]

Thuerauf DJ, Hanford DS, Glembotski CC. Regulation of rat brain natriuretic peptide transcription. A potential role for GATA-related transcription factors in myocardial cell gene expression. J Biol Chem. 1994; 269:17772–17775. [PubMed: 8027030]

Tsuji T, Kunieda T. A loss-of-function mutation in natriuretic peptide receptor 2 (Npr2) gene is responsible for disproportionate dwarfism in cn/cn mouse. J Biol Chem. 2005; 280:14288–14292. [PubMed: 15722353]

Vanneste Y, Michel A, Dimaline R, Najdovski T, Deschodt-Lanckman M. Hydrolysis of alpha-human atrial natriuretic peptide in vitro by human kidney membranes and purified endopeptidase-24.11. Evidence for a novel cleavage site. Biochem J. 1988; 254:531–537. [PubMed: 2972276]

Vieira MA, Gao M, Nikonova LN, Maack T. Molecular and cellular physiology of the dissociation of atrial natriuretic peptide from guanylyl cyclase a receptors. J Biol Chem. 2001; 276:36438–36445. [PubMed: 11479286]

Wang DJ, Dowling TC, Meadows D, Ayala T, Marshall J, Minshall S, Greenberg N, Thattassery E, Fisher ML, Rao K, Gottlieb SS. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. Circulation. 2004; 110:1620–1625. [PubMed: 15337695]

Wang Y, de Waard MC, Sterner-Kock A, Stepan H, Schultheiss HP, Duncker DJ, Walther T. Cardiomyocyte-restricted over-expression of C-type natriuretic peptide prevents cardiac hypertrophy induced by myocardial infarction in mice. Eur J Heart Fail. 2007; 9:548–557. [PubMed: 17407830]

Wilcox JN, Augustine A, Goeddel DV, Lowe DG. Differential regional expression of three natriuretic peptide receptor genes within primate tissues. Mol Cell Biol. 1991; 11:3454–3462. [PubMed: 1646390]

Witteles RM, Kao D, Christopherson D, Matsuda K, Vagelos RH, Schreiber D, Fowler MB. Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction a randomized, double-blind, placebo-controlled clinical trial. J Am Coll Cardiol. 2007; 50:1835–1840. [PubMed: 17980248]

Wu C, Wu F, Pan J, Morser J, Wu Q. Furin-mediated processing of Pro-C-type natriuretic peptide. J Biol Chem. 2003; 278:25847–25852. [PubMed: 12736257]

Yan W, Wu F, Morser J, Wu Q. Corin, a transmembrane cardiac serine protease, acts as a pro-atrial natriuretic peptide-converting enzyme. Proc Natl Acad Sci U S A. 2000; 97:8525–8529. [PubMed: 10880574]

Yandle TG, Brennan SO, Espiner EA, Nicholls MG, Richards AM. Endopeptidase-24.11 in human plasma degrades atrial natriuretic factor (ANF) to ANF(99–105/106–126). Peptides. 1989; 10:891–894. [PubMed: 2531377]

Yandle TG, Richards AM, Nicholls MG, Cuneo R, Espiner EA, Livesey JH. Metabolic clearance rate and plasma half life of alpha-human atrial natriuretic peptide in man. Life Sci. 1986; 38:1827–1833. [PubMed: 2939312]

Yasoda A, Komatsu Y, Chusho H, Miyazawa T, Ozasa A, Miura M, Kurihara T, Rogi T, Tanaka S, Suda M, Tamura N, Ogawa Y, Nakao K. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. Nat Med. 2004; 10:80–86. [PubMed: 14702637]

Yeung VT, Ho SK, Nicholls MG, Cockram CS. Binding of CNP-22 and CNP-53 to cultured mouse astrocytes and effects on cyclic GMP. Peptides. 1996; 17:101–106. [PubMed: 8822517]

Yoder AR, Kruse AC, Earhart CA, Ohlendorf DH, Potter LR. Reduced ability of C-type natriuretic peptide (CNP) to activate natriuretic peptide receptor B (NPR-B) causes dwarfism in lbab −/− mice. Peptides. 2008; 9:1575–1581. [PubMed: 18554750]

Yoshimura M, Yasue H, Morita E, Sakaino N, Jougasaki M, Kurose M, Mukoyama M, Saito Y, Nakao K, Imura H. Hemodynamic, renal, and hormonal responses to brain natriuretic peptide infusion in patients with congestive heart failure. Circulation. 1991; 84:1581–1588. [PubMed: 1914098]

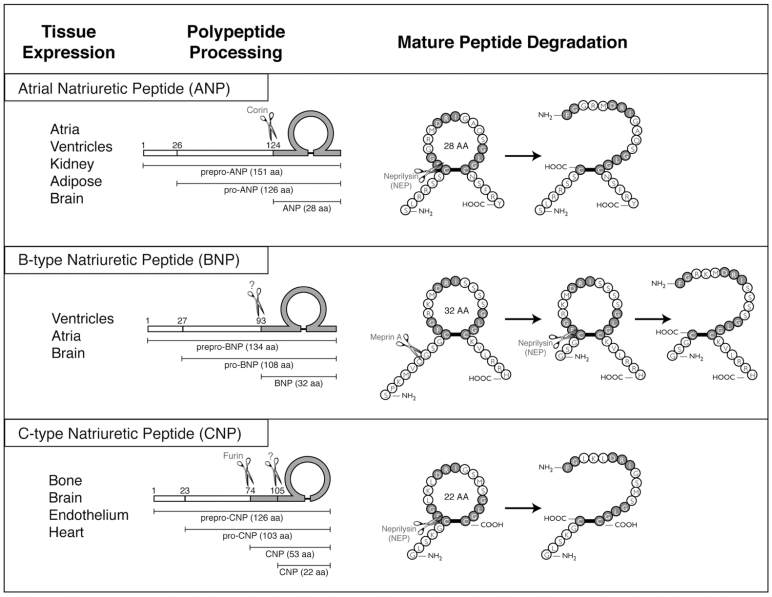

Fig. 1.

Structure of the human natriuretic peptides. The structure of the preprohormones for ANP, BNP and CNP are outlined on the left of each panel. The final amino acid sequence and structure of the mature peptides along with the major degradation product are shown on the right. The sites of cleavage are indicated with scissors.

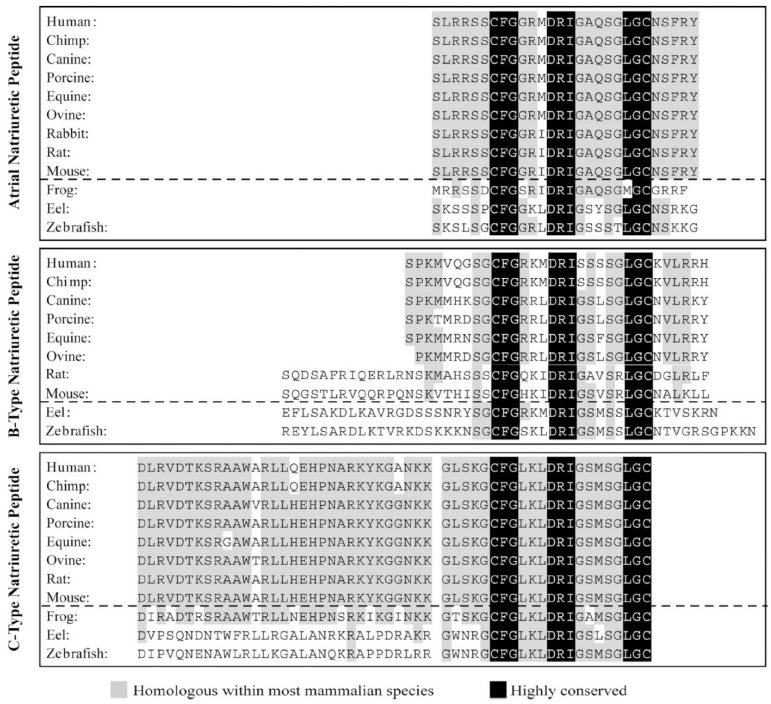

Fig. 2.

Sequence alignment of natriuretic peptides. The sequences for the species listed above were obtained from the NCBI Entrez Protein database. The accession numbers for the above sequences (from top to bottom) are: for ANP [NP_006163.1; XP_001141705.1; XP_850357.1; NP_999425.1; NP_999425.1; NP_001075970.1; AAB92564; NP_001075731.1; NP_036744.1; NP_03275.1; P18909; BAA34122; NP_942095], for BNP [NP_002512.1; XP_525186.2; XP_544566.2; P07634; ABG91577; AAB92565; NP_113733.1; NP_032752.1; BAE19674; XP_696498], and for CNP [NP_077720.1; XP_001141992.1; XP_852684.1; NP_001008482.1; XP_001498652; NP_001009479; NP_446202.1; NP_035063.1; BAA04236; BAA13529; XP_692388]. For ANP, the mature circulating form for all mammalian species is 28 amino acid as shown; the same size peptide is shown for the non-mammalian species for comparison purposes only. For BNP, the mature circulating form varies as shown. For CNP, the 53-amino acid form is shown for all.