The natriuretic peptides (NPs) are a group of peptide hormones that play important roles in the control of renal, cardiovascular, endocrine, and skeletal homeostasis. Atrial NP (ANP) was first identified as an activity by de Bold et al.1 in 1981. It is a 28 amino acid peptide in humans that assumes a hairpin structure by virtue of a cystine bridge that links residues 7 and 23 (Figure 1). Brain NP (BNP), also known as the B-type NP, is a 32 amino acids long in the human. It has a similar hairpin structure but demonstrates considerably more heterogeneity across species than ANP. C-type NP (CNP) is a 22 amino acid peptide that has a truncated carboxy terminus beyond the second cysteine residue in the bridge.

ANP and BNP are produced primarily within the muscle cells of the heart. ANP shows a preference for expression in the cardiac atria versus ventricle, whereas BNP is more equivalently expressed throughout the heart. ANP is also expressed in the hypothalamus where it is thought to control blood pressure (BP), sympathetic outflow, vasopressin secretion, drinking behavior, and cardiovascular homeostasis. BNP, on the other hand, is expressed in the brains of only a few species (eg, pig and dog), where its function remains unknown. CNP is expressed in the central nervous system, reproductive tract, bone, and endothelium of blood vessels.

There are 3 different types of NP receptors, and each of them spans the membrane bilayer as a single transmembrane segment. The type A NP receptor (NPR-A) is also known as the particulate guanylyl cyclase A. It is the high affinity receptor for both ANP and BNP. A schematic of the structure of this receptor is presented in Figure 2. NPR-A has a glycosylated, extracellular, ligand-binding domain linked to a hydrophobic transmembrane spanning segment, a noncatalytic, ATP-binding, kinase-like domain linked to a variety of other peptides with more distant structural homology. The type A NP receptor has a particulate guanylyl cyclase that is the catalytic effector of the receptor. Association of NPR-A with its cognate ligand (ANP or BNP) causes a conformational change in the kinase-like domain, which relaxes tonic inhibition of guanylyl cyclase activity and increases production of cGMP. NPR-B shares a similar structure with NPR-A. It binds selectively to CNP. NPR-C, the so-called clearance receptor, has an extracellular domain that is structurally homologous to that of the other NPRs. This is linked to a single transmembrane-spanning segment followed by an intracellular domain containing only 37 amino acids. NPR-C binds with high affinity to all 3 NPs, as well as to a variety of other peptides with more distant structural homology. The primary role of NPR-C is to function in a clearance mode, capturing and degrading NPs in the extracellular compartment.2

Earlier reviews have dealt with the regulators of NP gene expression.3 This brief review will focus on the molecular details underlying the transcriptional regulation of these genes and those of their receptors and the use of genetic models to dissect out their respective contributions to normal and abnormal cardiovascular and renal function.

Transcriptional Regulation of the NP Genes
NP gene expression is controlled by a number of factors, including α-adrenergic agonists, endothelin (ET), prostaglandin \( \text{F}_2\alpha \), growth factors, vitamin D, retinoids, glucocorticoids, mechanical strain, and hypoxia, among others. It is noteworthy that factors that increase ANP and BNP gene expression are also commonly linked to myocyte hypertrophy. A plethora of studies carried out over the last 15 years have confirmed that NP gene expression is one of the most highly conserved markers of hypertrophy-dependent gene transcription in different pathophysiological states, across species. This reflects a reversion of the hypertrophied myocyte transcriptional profile back to the fetal program.4

Transcription of the rat ANP and BNP genes is under control of the GATA transcription factor family (factors that bind to the sequence \( \text{A/TGATAA/G} \), particularly GATA-4 and GATA-6. Paired GATA sites are located at \( -280 \) and \( -120 \) relative to the transcription start site of the rat (r) ANP gene.5 GATA binding elements have also been identified in the rat and human BNP gene promoter6–9 with paired sites at \( -96 \) and \( -84 \) in the rat gene, relative to the start site of transcription, and similarly positioned sites in the human gene. Mutation of GATA binding sites leads to a reduction in rat or human BNP gene promoter activity,\(^{5,9,10}\) and forced expression of GATA-4 leads to increased expression.\(^{8,9,11}\) GATA is phosphorylated on Ser\(_{\text{475}}\) by p38 mitogen-activated protein kinase (MAPK). This phosphorylation results in

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Molecular Biology of the Natriuretic Peptide System
Implications for Physiology and Hypertension

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increased binding of GATA to DNA and activation of contiguous gene transcription. GATA binding sites in the BNP gene promoter have been linked to the stimulatory activity of lipopolysaccharide, β adrenergic agonists, ET (operating through a Rho kinase signaling pathway), and mechanical strain/hemodynamic overload. GATA-4 has been shown to establish physical contact and to functionally synergize with GATA-6, MEF-2, dHAND, SRF, Nkx2.5, and YY1. In the case of dHAND, YY1, and GATA-5, functional synergy appears to occur by virtue of recruitment of the transcriptional coactivators p300 and CBP into the complex. The friend of GATA (FOG-2), a transcriptional corepressor that binds specifically to GATA-4, has been shown to interact with chicken ovalbumin upstream promoter transcription factor 2 (COUP-TF2) and to prevent activation of the chicken ANP gene promoter. FOG-2 has similarly been shown to reduce BNP reporter activity in neonatal cardiac myocytes. The basic helix–loop–helix transcription factor Hey represses GATA-4 and GATA-6 function in the mouse heart, thereby reducing ANP gene expression. Jumonji is thought to mediate its inhibition of rANP gene transcription through direct interaction with and subsequent inhibition of GATA-4 and Nkx2.5. GATA-independent interactions (eg, between dHAND and MEF-2c and between PITX2 and MEF2A) on the ANP gene promoter have also been documented. Consistent with the in vitro observations, cardiac-specific deletion of GATA4 results in diminished ANP gene expression and impairment in the hypertrophic response.

The rat ANP gene promoter is also regulated by the homeodomain protein Nkx2–5 and the T box factor Tbx5, both of which have binding sites in the proximal 5' flanking sequence of the ANP gene. Nkx 2–5 associates with an NKE2 site positioned at −240 in the rat ANP gene, Tbx5 associates with TBEs at −485, −252, and −90 in the rat ANP gene, and homologous binding elements have been identified in the human and mouse genes. Tbx5 has been shown to cooperate with Nkx2–5 in promoting ANP gene transcription. Nkx2–5 appears to function, at least in part, through association with calmodulin-binding transcription activators. Mice homozygous for deletion of the calmodulin-binding transcription activator gene are defective in the cardiac growth response to hemodynamic overload and neurohormonal signaling.

A transgenic analysis of the Xenopus ANP promoter, carried out using frog embryos, identified an NKE, 2 GATA binding sites, a TBE, and 2 serum response factor-binding sites (SREs), all with homologues in the human gene promoter. Mutation of the individual sites, alone or in combination, demonstrated that the SREs, TBE, and distal GATA site are important for maintenance of basal transcription of the ANP promoter. Although the proximal GATA site and NKE contribute quantitatively to promoter activity, they are equally important for maintenance of temporal and spatial expression of the ANP gene in the heart.

Members of the extended Jun/Fos transcription factor family (including c-jun, jun B, jun D, c-fos, fra 1, and fra 2), have been shown to participate in the transcriptional regulation of the ANP and BNP genes through the activator protein 1 binding site. Individual members of the Jun and Fos family display differential activity at the level of the human (h)ANP promoter, but the presence of the activator protein 1 site in the hANP gene promoter is required for basal transcriptional activity. Interestingly, the rat ANP gene, unlike its...
human counterpart, appears to be negatively regulated by both c-Jun and c-Fos.37 There is a Fos- but not Jun-activatable activator protein 1 binding element in the rat gene promoter (Jun is thought to promote association of Fos with the promoter) that is potentiated by stimulation of the MAPK44 pathway. Candidate activator protein 1 sites have been identified at −110 in the rBNP gene and at −109 in the hBNP gene.38 Mutation of these sites leads to reductions in basal promoter activity.38 (F. Wang and D.G. Gardner, unpublished observations, 2003).

Transcription enhancing factor (or M-CAT) binding elements have been identified in the 5′ flanking sequence of the BNP gene (−110 in rats with paired sites at −123 and −94 in humans). Mutation of these sites results in a significant decrease in basal promoter activity.6,39 Mutation of the rat M-CAT site suppresses α adrenergic agonist-dependent rBNP promoter activity,39 implying that this site is involved in trafficking the agonist-dependent signal.

An Ets binding site at position −498 in the rBNP gene traffics ET-dependent promoter activity through a p38 MAPK pathway.40 An E box motif upstream (−1152) in the hBNP gene has been shown to harbor transcriptional repressor activity,41 but its regulatory capacity remains unknown.

A neuron restrictive silencer element in the 3′ untranslated region of the rat ANP gene regulates both basal and ET-dependent gene transcription in ventricular myocytes.42 A similar neuron restrictive silencer element has been identified upstream from the transcription start site6,43 in the hBNP gene promoter. Mutation of the hBNP neuron restrictive silencer element reduces basal promoter activity and blunts the transcriptional response to fibronectin. Neuron restrictive silencer factor, which binds to the neuron restrictive silencer element, is believed to control expression of the fetal gene program, a transcriptional hallmark of myocyte hypertrophy.44 Transgenic mice that overexpress a dominant-negative mutant of neuron restrictive silencer factor display dilated cardiomyopathy and increased susceptibility to arrhythmias and sudden death.44

SRE has been identified and confirmed to have functional activity in both the rat and human ANP genes.5,18,45 Mutation of the SRE at −241 in the human promoter reduces basal activity and impairs the response to ET. In this instance, ET signals through a Src-45 and p130 Cas-dependent pathway.46

Mechanical strain, or its in vivo correlate hemodynamic load, is thought to be a major regulator of NP gene transcription. The ability of mechanical strain to activate BNP gene transcription in vitro has been shown to reside with 3 shear stress response element-like structures in the 5′ flanking sequence of that gene (located at −650, −641, and −160). Mutation of these sites results in ∼50% reduction in strain-dependent hBNP promoter activity, as does inhibition of p38 MAPK and nuclear factor κB–dependent signaling pathways. This implies that p38 MAPK and nuclear factor κB ultimately signal increased promoter activity through the SREs.47,48 The strain response has also been linked to the presence of intact GATA binding sites in the proximal promoter.14

Mutation of a nuclear factor of activated T cells (NF-AT) binding site at −927 in the human BNP gene has been shown to inhibit ET-dependent activation of the BNP promoter.49 Molkentin et al49 interpreted this, as well as a number of parallel findings, as implicating the calcineurin/NF-AT pathway as a key contributant to hypertrophy-dependent gene transcription in the cardiac myocyte.

A number of nuclear receptors (eg, vitamin D receptor, peroxisome proliferator activated receptor, retinoic acid, and retinoid X receptors) have been shown to reduce basal and agonist-stimulated ANP and BNP gene transcription. The inhibitory promoter loci for the 1,25-dihydroxyvitamin D3 receptor50,51 and peroxisome proliferator activated receptor α are located in the proximal 5′ flanking sequence of the hANP and/or hBNP genes. A thyroid hormone receptor binding element (TRE) has been identified at ∼1 kb upstream from the transcription start site in the hBNP gene. This element associates with the liganded thyroid hormone receptor in vitro and signals thyroid hormone–dependent stimulation of BNP promoter activity52 in the intact cell.

Deschepper et al53 have recently linked heritable differences in ANP gene transcriptional activity to a specific phenotype in genetically inbred rat strains. They found that DNA sequence differences in the proximal rat ANP promoter are associated with reduced promoter activity (assessed in transiently transfected neonatal rat cardiac myocytes in vitro) and, consequently, diminished ANP gene expression in the Wistar–Kyoto hyperactive versus Wistar–Kyoto rat. Wistar–Kyoto hyperactive rats have significantly larger hearts relative to the Wistar–Kyoto, and the authors relate this hypertrophy to reduced ANP gene expression in the cardiac myocyte. Interestingly, polymorphisms in the promoter of the human NPR-A gene have been linked with left ventricular mass in human essential hypertension.34 These studies add to a growing body of data,55–61 (see below) suggesting that the NPs exert protective, antihypertrophic activity in the myocardium.

Regulation of CNP gene (Nppc) transcription has been less well studied than ANP and BNP. Like that of its cognate receptor62 (see below), the CNP gene requires GC-rich regions in the proximal promoter to support basal transcriptional activity.63 The murine CNP gene is positively regulated by the Wnt signaling pathway, operating through β-catenin and T-cell factor/lymphoid enhancer binding factor, which specifically associate with cognate elements in the proximal promoter.64 It appears that TSC-22, a transforming growth factor β–stimulated transcription factor, also plays a role in controlling CNP gene transcription.65

**Regulation of the NP Receptors**

As shown in Figure 2, the 3 NP receptors differ in structure, biological effects, and ligand specificity. Partial structures of NPR-A and NPR-C have been solved, revealing important details of the respective receptor–ligand interactions. Genomic structure of mouse, rat, and human NPR-A; human NPR-B; and mouse and human NPR-C have been reported; however, relatively little information exists regarding their regulation.

Regulation of rat NPR-A gene transcriptional activity is governed by 3 Sp1 binding sites (at −341, −282, and −56) in the promoter.66,67 Mutation of these sites results in >90% reduction in promoter activity. Liang et al66 demonstrated that
these Sp1 sites interact synergistically with a nuclear factor Y (NF-Y) binding site (at −141) to control >95% of basal promoter activity in rat aortic smooth muscle cells. Overexpression of Ets-1 in mouse mesangial cells increases NPR-A gene transcription 12-fold, whereas overexpression of GATA-1 or Lyf-1 results in a 50% and 80% reduction in promoter activity, respectively.68 Mutation or deletion of the c-Ets binding elements positioned at approximately −45 and −14 in the murine gene leads to a loss of the Ets-1–dependent induction.68 A series of Sp1 sites positioned between −118 and −83 in the human NPR-B gene play a dominant role in the regulation of that gene’s basal promoter activity.62

NPR-A activity, NPR-A gene expression, and NPR-A promoter activity are negatively regulated by its cognate ligand ANP (homologous down regulation) through a mechanism that appears to require cGMP.69 This agonist-mediated down regulation requires sequence positioned between −1575 and −1290 relative to the transcription start site. This region contains the sequence AaTrKaNTTCaAcAKTY, which may represent the cGMP-dependent regulatory element in this gene.70

NPR-A is also regulated by 1,25 dihydroxyvitamin D through a single vitamin D response element between −498 and −484 in the promoter. This vitamin D–dependent induction of NPR-A expression may account for at least some of the salutary effects of vitamin D in the cardiovascular system.71 NPR-A gene promoter activity has also been shown to be negatively regulated by angiotensin II72 and positively regulated by osmotic stimuli.73 The latter effect involves the endothelial NO synthase and p38 MAPK.74

**Genetic Manipulation of the NP Systems**

The availability of genetically manipulated mouse models has allowed for detailed investigation of the physiology of the NP systems and their potential contribution to hypertension and other cardiovascular disease (see the Table). Hepatic overexpression of the mouse ANP gene (using the transthyretin gene promoter) results in plasma ANP levels that are increased >8-fold.75 BP is reduced by 30 mm Hg without an increase in urinary sodium excretion or an increase in urinary volume. Mice expressing the ANP transgene maintain normal salt excretion despite reduced BP,76 presumably reflecting direct effects of ANP on glomerular hemodynamics or tubular sodium transport. Volume expansion is accompanied by a significantly greater increase in urinary volume and sodium excretion in the ANP transgenics versus controls. These animals also displayed increased water intake and excretion presumably reflecting ANP-dependent antagonism of vasopressin-induced water permeability in the terminal nephron.77

Mice with homozygous deletion of the ANP gene locus have no circulating or atrial ANP.78 BPs increased by 8 and 23 mm Hg when animals were fed standard (0.5%) or intermediate (2%) NaCl diets. Mice heterozygous for the deletion had normal BP on the standard diet but were hypertensive (27 mm Hg increase in BP) on 8% NaCl; however, subsequent studies suggested that salt sensitivity is not uniformly present in these mice.79 When present, salt sensitivity may result from incomplete suppression of plasma renin activity.80 Homozygous mutants have right and left ventricular hypertrophy under basal conditions, and this is increased disproportionately (relative to controls) in response to transverse aortic constriction.81 Hypertrophy is accompanied by increased expression of a variety of extracellular matrix proteins (eg, osteopontin) and metalloproteinases (eg, matrix metalloproteinase-2), implying that ANP negatively regulates matrix remodeling in the myocardium. Normalization of BP in the ANP knockout animals through administra-

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**Summary of the Phenotypes Associated With Genetic Manipulation of the NP System**

<table>
<thead>
<tr>
<th>Gene Disruption</th>
<th>Phenotype/Physiology</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP overexpression</td>
<td>Hypotension, decrease in hypoxic hypertension, normal salt excretion, increased H2O intake and excretion</td>
<td>75–77</td>
</tr>
<tr>
<td>ANP knockout (Nppa−/−)</td>
<td>Hypertension, BP-independent right and left ventricular hypertrophy, impaired Na and Cl excretion</td>
<td>78–83</td>
</tr>
<tr>
<td>BNP overexpression</td>
<td>Hypotension, skeletal overgrowth, resistance to immune-mediated renal injury</td>
<td>84–86</td>
</tr>
<tr>
<td>BNP knockout (Nppb−/−)</td>
<td>Load dependent ventricular fibrotic lesions, no hypertrophy, no hypertension</td>
<td>87</td>
</tr>
<tr>
<td>CNP knockout (Nppc−/−)</td>
<td>Dwarfism, early death</td>
<td>88</td>
</tr>
<tr>
<td>CNP overexpression (chondrocyte targeted)</td>
<td>Rescue of dwarfism phenotype</td>
<td>89</td>
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<tr>
<td>NPR-A (GC-A) overexpression</td>
<td>Hypotension, protection against salt-sensitive hypertension</td>
<td>92</td>
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<tr>
<td>NPR-A (GC-A) knockout (Npr1−/−)</td>
<td>Salt-resistant hypertension, BP-independent ventricular hypertrophy, increase in sudden death, enhanced NHE-1 activity, increased susceptibility to heart failure</td>
<td>55,58,59,90,91</td>
</tr>
<tr>
<td>NPR-A targeted knockout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyocyte</td>
<td>Hypertrophy, increase in hypertrophy markers, hypotension</td>
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<tr>
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<td>Loss of ANP response, volume dependent hypertension</td>
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<tr>
<td>Vascular endothelium</td>
<td>Arterial hypertension and cardiac hypertrophy, increased plasma volume</td>
<td>98</td>
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<tr>
<td>NPR-B (GC-B) knockout (Npr2−/−)</td>
<td>Dwarfism, neuronal disorders, female infertility</td>
<td>100</td>
</tr>
<tr>
<td>NPR-B (GC-B) dominant-negative overexpression (rat)</td>
<td>BP-independent cardiac hypertrophy, increased congestive heart failure, elevated heart rate</td>
<td>102</td>
</tr>
<tr>
<td>NPR-C knockout (Npr3−/−)</td>
<td>Hypotension, bone overgrowth, reduced blood volume</td>
<td>103</td>
</tr>
</tbody>
</table>
tion of a low-salt diet failed to reverse the hypertrophy, suggesting that ANP exerts a direct antihypertrophic effect on the cardiac myocyte, a hypothesis that has found support in a number of in vitro and in vivo studies. Mice homozygous for the ANP gene deletion also display an impaired diuretic response to acute saline infusion. BPs were higher in the knockouts versus controls, but glomerular filtration rates were not different. Despite this, the knockouts had limited capacity to excrete the sodium load, suggesting inappropriate reabsorption of these ions in the medullary collecting duct. Thus, it appears that ANP reduces BP without significantly altering urinary sodium excretion under basal, steady state conditions, and ANP is not essential for maintenance of normal salt balance but is essential for excretion of the sodium load that accompanies acute expansion of intravascular volume.

Forced expression of a mouse BNP transgene under the control of the liver-specific human serum amyloid P component promoter results in plasma BNP levels that are 10- to 100-fold elevated over wild-type controls, and this is accompanied by a significant reduction in BP and an increase in plasma cGMP levels relative to their nontransgenic littermates. Interestingly, as they aged, these mice developed pronounced skeletal overgrowth resulting in marked kyphosis of the spine, elongation of limbs, and crooked tails. Subsequent analyses showed that BNP increases the height of the cartilaginous primordium leading to increased longitudinal bone growth. Suganami et al. have shown that BNP transgenic mice display resistance to immune-mediated renal injury. These animals have less albuminuria and improved histological and functional scores relative to wild-type animals after renal injury.

Unlike the ANP gene-deleted mice, those with deletion of the BNP gene display no hypertension or ventricular hypertrophy. They demonstrate multifocal fibrotic lesions in the cardiac ventricles, which were amplified in size and number in response to ventricular overload. These findings have led to the hypothesis that BNP subserves a role as an antifibrotic factor in vivo. The disparate effects of ANP versus BNP in the myocardium remain, to some degree, paradoxical in that both are believed to signal exclusively through the same NPR-A receptor.

Deletion of the murine CNP gene results in somatic dwarfism and early death. The skeletal phenotypes were similar to those seen in human achondroplasia with impairment of endochondral ossification. Targeted expression of CNP to the chondrocytes of the endochondral growth plate rescued the skeletal phenotype of the Nppc−/− mice and prolonged their survival. Of note, targeted overexpression of CNP in chondrocytes was later shown to rescue the dwarfed phenotype in an independent mouse model of achondroplasia because of activated fibroblast growth factor receptor 3 in cartilage.

Homozygous deletion of the type A NP receptor (NPR-A or guanylyl cyclase A/guanylyl cyclase A receptor) results in salt-resistant hypertension, cardiac hypertrophy, and an increased incidence of cardiac sudden death. Myocyte hypertrophy in these mice has been linked to increased activity of the Na+/H+ exchanger NHE1. BPs in these animals are directly proportional to the number of copies of the NPR-A gene present. Deletion of the NPR-A gene results in the loss of virtually all cardiovascular effects of ANP and BNP, suggesting that these peptides signal their physiological activity almost exclusively through the NPR-A receptor. As noted above with the ANP gene-deleted mice, NPR-A knockout mice display normal ability to respond to changes in dietary sodium concentration but impaired ability to initiate a natriuretic response to acute iso-oncotic volume expansion. These mice also have an increased susceptibility to heart failure after creation of aortocaval fistulas. The ventricular hypertrophy seen in these NPR-A−/− mice appears to reflect, in large part, the loss of a direct antihypertrophic effect of the liganded NPR-A in the heart. Pharmacological control of BP in these animals fails to reverse left ventricular hypertrophy, and the mice hyperrespond to transverse aortic constriction with increased left ventricular thickness and activation of ANP gene expression (a transcriptional marker of hypertrophy) relative to wild-type controls.

Cardiac-specific overexpression of NPR-A in the hearts of the NPR-A knockout mice results in reductions in myocyte size and ANP gene expression. Finally, targeted deletion of the NPR-A gene locus in the heart, using a Cre-Lox strategy, results in mild hypertrophy and increased expression of the fetal gene program (ie, ANP, α skeletal actin, and β myosin heavy chain), which serves as a transcriptional marker of hypertrophy. BPs are lower in these latter animals, likely reflecting the peripheral hormonal effects of elevated circulating ANP levels.

Selective deletion of the NPR-A gene in smooth muscle cells has no net effect on systemic BP under basal conditions, but it does prevent the hypertensive response to infused ANP. Acute increases in intravascular volume lead to a rapid and significant increase in BP in the NPR-A gene-deleted mice but not in wild-type mice, presumably reflecting loss of the hypertensive effects of endogenous ANP. Selective inactivation of the NPR-A gene in vascular endothelium leads to systemic hypertension and cardiac hypertrophy and abrogation of the ANP-dependent contraction of intravascular volume in the mouse (reflecting extravasation of fluid into the interstitial compartment). Inactivation of the NPR-A gene also alleviates ischemia/reperfusion injury through suppression of nuclear factor kβ-mediated P-selectin induction, as does the NPR-A antagonist HS-142-1, a property that might prove useful in limiting reperfusion injury clinically.

NPR-B gene-deleted mice are small relative to their wild-type littermates with dysfunctional endochondral ossification and diminished longitudinal growth in vertebra and limbs. Developmental abnormalities in the female reproductive tract appear to be responsible for the observed impairment in female fertility. NPR-B gene-deleted mice were not hypertensive under a variety of salt-loading paradigms. It is worth noting that mutations in the human NPR-B gene have been associated with Maroteaux-type acromesomelic dysplasia. This clinical observation lends further support to the link between the CNP/NPR-B system and normal growth in the long bones of the skeleton. Transgenic rats expressing a dominant-negative mutant of NPR-B in the heart display progressive BP-independent cardiac hypertrophy and ele-
vated heart rate, implying that CNP plays an important role in controlling myocyte growth in vivo\textsuperscript{102}. Deletion of the NPR-C gene leads to low BP (8 mm Hg below normal), mild diuresis, and reduced blood volume, a phenotype that likely reflects the longer half-life of endogenous NPs. These animals also have a bone phenotype that is similar to that seen in the BNP transgenics (ie, exaggerated bone growth in the tail and spine). In this case, it is thought to reflect impaired clearance and, inferentially, amplified activity of locally synthesized CNP.\textsuperscript{103}

**Perspectives**

A combination of pharmacological studies and careful examination of genetic models (see the Table) have shown that the NPs play important roles in the regulation of cardiovascular, renal, and skeletal homeostasis. Of equal importance, dysregulation of the NP signaling systems appears to contribute to the pathophysiology of clinical disorders affecting these different systems. Measurement of plasma NP levels is now being used to assist in the diagnosis of a variety of cardiovascular diseases, to assign risk for the development of disease in different populations, and to assess prognosis. Clinically, recombinant BNP is being used in the management of acute heart failure. A better understanding of the function and regulation of these NP systems may provide an opportunity to develop additional tools for use in the diagnosis and management of clinical disease.

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**Disclosures**

None.

**References**


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