Guanylyl Cyclase-Linked Natriuretic Peptide Receptors: Structure and Regulation

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The abbreviations used are: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; HEK, human embryonic kidney; KHD, kinase homology domain; NP, natriuretic peptide; NPR-A, natriuretic peptide receptor A; NPR-B, natriuretic peptide receptor B; PAGE, polyacrylamide gel electrophoresis; PKC, protein kinase C; PMA, phorbol 12-myristate 13-acetate.
In 1956, two seemingly disparate, but profoundly prophetic papers were published. Kisch observed that atrial, but not ventricular, cardiac cells contain a highly developed Golgi network, reminiscent of a secretory system (1), and Henry and colleagues discovered that elevated left atrial pressure stimulates urine output (2). Twenty-five years later the connection between these studies and the heart and the kidney was made when de Bold and colleagues determined that rat atrial extracts contain a potent diuretic and natriuretic factor (3). Since the publication of this landmark paper in 1981, three structurally related but genetically distinct peptides with vasodilatory properties, called atrial natriuretic factor (ANF), also known as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) have been purified and molecularly cloned (4,5) (Fig. 1).

The primary signaling molecules for these hormones are natriuretic peptide receptor-A (NPR-A) and natriuretic peptide receptor-B (NPR-B) (Fig. 1). They are members of the cell-surface family of guanylyl cyclase receptors, enzymes that catalyze the synthesis of the intracellular second messenger, cGMP (5,6). Hence, they are sometimes referred to as guanylyl cyclase-A and guanylyl cyclase-B or GC-A and GC-B. NPR-A is activated by physiologic concentrations of ANP and BNP, but not CNP (7,8). Conversely CNP, but not ANP or BNP, activates NPR-B (7,8). In addition, all three natriuretic peptides bind the natriuretic peptide clearance receptor (NPR-C). In many tissues, NPR-C is the most abundant of the three natriuretic peptide receptors, and it binds ANP, BNP and CNP with relatively similar affinities.
It has only 37 intracellular amino acids and does not possess guanylyl cyclase activity. It is thought to primarily control the local concentrations of natriuretic peptides that are available to bind NPR-A and NPR-B (9), but a signaling function for this receptor has also been reported (10). In this review, we summarize the available data on the structure and regulation of NPR-A and NPR-B.

**Receptor Structure, Topology and Oligomeric State**

The basic topology of NPR-A and B consists of an approximately 450-amino acid extracellular ligand-binding domain, a 21-residue hydrophobic membrane-spanning region, and a 566-or 568-amino acid intracellular domain, respectively (Fig. 1). The latter can be further divided into a juxta-membrane region of approximately 250-amino acids that is similar to known protein kinases called the kinase homology domain (KHD), a 41-amino acid amphipathic coiled-coiled hinge region, and a roughly 250-amino acid carboxyl-terminal guanylyl cyclase catalytic domain. In the absence of ligand, NPR-A exists as a homodimer or homotetramer, and ANP binding does not lead to further aggregation (11-13). Multiple domains that are located both outside and inside the plasma membrane mediate the oligomerization of NPR-A. The intracellular dimerization interface region has been mapped to the amphipathic sequence that bisects the KHD and cyclase domains (14). The deletion of this region results in monomeric and inactive intracellular constructs, suggesting that dimerization of the cyclase domains is required for catalytic activity. NPR-B is also an oligomer in the absence of ligand (15).
The disulfide bonding structure of an extracellular secreted version of rat NPR-A has been determined (16). In this receptor, intramolecular bonds were found between Cys60-Cys86, Cys164-215 and Cys423 and Cys432. Hence, the NPR-A extracellular domain contains three intramolecular but no intermolecular disulfide bonds. Two groups have addressed the role of the juxtamembrane cysteines in NPR-A. Labrecque et al. found that the conversion of Cys423 to serine resulted in a receptor variant that migrated at twice the molecular weight of the wild-type receptor under nonreducing, but not reducing SDS-PAGE conditions (17). They concluded that the removal of Cys423 allowed Cys432 to form an intermolecular disulfide bond with the corresponding residue on a separate polypeptide chain. This mutant’s basal activity is elevated 20-40 fold compared to the wild-type receptor, but has a diminished ability to be activated by ANP and/or ATP. In a separate experiments, Huo and colleagues found that the mutation of both Cys423 and Cys432 to serine results in a variant with similar guanylyl cyclase properties as the single Cys423 mutant (18). Together, these data emphasize the importance of the juxtamembrane intrachain disulfide bond in NPR-A activation, and suggest the increased basal activity observed with the Cys423 mutant results from the loss of an intramolecular disulfide bond, not from the creation of an intermolecular disulfide bond. Studies of the disulfide binding pattern of NPR-B have not been reported, but since the cysteines involved in the amino-terminal (Cys53 and Cys79) and juxtamembrane disulfide bonds (Cys417 and Cys426) are conserved between NPR-A and NPR-B, it is likely that these bonds form in NPR-B as well. A middle
disulfide bond might be formed between Cys205 and Cys314, since these are the only remaining Cys in the extracellular domain of this receptor.

The crystal structure of the glycosylated, unliganded, dimerized hormone-binding domain of NPR-A has been solved at 2.0 Å resolution (19). The monomer consists of two interconnected subdomains, each encompassing a central β-sheet flanked by α-helices, and exhibits a type I periplasmic binding-protein fold. Dimerization appears to be mediated by juxtaposition of 2x2 parallel helices that bring the two protruding carboxyl-termini in close proximity. Affinity labeling experiments indicated that residues 4 and 18 of ANP bind in the vicinity of Met173 of NPR-A and that the carboxyl terminus of ANP binds near His195. The assignment of receptor contact residues by the crystallography group is consistent with a previous report demonstrating that the amino portion of ANP could be cross-linked to the NPR-A chymotryptic peptide Met173 to Phe188 (20). The structure of an ANP-NPR-A complex has not been solved, but Van den Akker et. al speculate that the dimeric receptor contains two spatially separated ANP binding sites, which yields a ligand-receptor stoichiometry of 2:2. This is consistent with previous studies that indicated the stoichiometry of binding is 1:1 (21,22) or 2:2 (23), but not with a study that suggested a stoichiometry of 1:2 (24). Perhaps the most surprising finding to come from the initial structural work on NPR-A is the presence of an apparent chloride-binding site buried within the amino-terminal portion of each monomer. Surprisingly, Misono reported that chloride is absolutely required for ANP binding to the
extracellular domain of NPR-A (25). Whether chloride is required for hormone binding to the full-length receptor or to NPR-B or NPR-C remains to be determined. In addition whether chloride binding is reversible, and therefore regulatory, also remains to be answered. However, since the chloride concentration that is necessary for 50% of the maximal ANP binding response (EC$_{50}$=0.6 mM) is two orders of magnitude below physiologic concentrations, this appears unlikely.

Presently, no direct data are available on the crystal structure of any guanylyl cyclase catalytic domain. However, due to the high sequence similarity between the catalytic domains of adenylyl and guanylyl cyclases, the latter have been molecularly modeled based on the coordinates from the former (26). Both cyclase domains appear to form a wreath-like structure with the mammalian adenylyl cyclases and soluble guanylyl cyclases containing one active site per heterodimer and the membrane guanylyl cyclases, including NPR-A and NPR-B, containing two active sites per homodimer (27). Because the residues that interact with ribose, triphosphate and Mg$^{2+}$ in adenylyl cyclase are conserved in guanylyl cyclases, it is believed they serve similar functions in both enzymes. Hence, the residues that interact with the purine base determine substrate specificity. In the model of the nucleotide-binding site of the retinal guanylyl cyclase (ret-GC-1 or GC-E), Glu925 and Cys997 are essential for nucleotide discrimination and are envisioned to form critical hydrogen bonds with the N1, N2 and O6 atoms of guanine, respectively (26). This model has now been tested and confirmed by Tucker and colleagues who
changed the substrate specificity of retinal guanylyl cyclase-1 from guanine to adenine by mutating Glu925 and Cys997 to Lys and Asp, the corresponding residues in adenylyl cyclases (28). These residues are conserved in NPR-A and NPR-B and are likely to serve similar functions in their active sites as well.

**Glycosylation**

NPR-A purified from transfected $^{35}$S-labeled 293 cells displays considerable size heterogeneity (13). The explanation for this variability is incomplete N-linked glycosylation since N-glycosidase treatment collapses all the higher molecular weight forms to a single species of approximately 116 kDa, the expected molecular mass of the core polypeptide (13). Direct sequencing of the amino termini of human NPR-IgG fusion proteins purified from CHO cells indicated that Asn2 and Asn13 of NPR-A and Asn2 of NPR-B are glycosylated (29). In Cos-1 cells, an extracellular truncation mutant of rat NPR-A was found to be glycosylated at positions Asn13, Asn180, Asn306, Asn347, and Asn395 (30). Asn2 is not conserved in the rat version of NPR-A. Enzymatic deglycosylation of the extracellular domain of NPR-A does not significantly affect its ANP binding properties (30). In contrast, Fenrick and colleagues determined that only the fully glycosylated form of NPR-B could be crosslinked to $^{125}$I-CNP (31). Furthermore, cotransfection with truncated versions of NPR-B or unrelated receptors that decreased the amount of the fully glycosylated form of NPR-B, presumably by saturating the cellular glycosylation machinery, reduced its ability to produce cGMP in response to CNP (31).
Mutational analysis of the asparagines present in the extracellular domain of bovine NPR-B suggested that five of the seven total sites are glycosylated, and the mutation of Asn2 reduced CNP-binding by 90%, presumably due to improper receptor folding (32). Collectively, these results suggest that glycosylation is required for proper receptor folding or targeting, but not for NP binding.

*Phosphorylation*

The first direct indication that NP receptors are regulated by protein phosphorylation came in 1992 when NPR-A purified from metabolically labeled HEK 293 cells was shown to contain $^{32}$P (33,34). The stoichiometry of phosphate to receptor molecules was not determined, but the fact that dephosphorylation resulted in a slight electrophoretic mobility shift indicated that it is at least 1:1 (33). Despite the homology of the NPR-A KHD to the tyrosine kinase domain of the platelet-derived growth factor (PDGF) receptor, phosphoamino acid analysis detected only phosphoserine and phosphothreonine (33-35). When whole cells or membrane preparations containing the NPR-A were incubated with ANP or the purified catalytic subunit of protein phosphatase 2A, respectively, the receptor was dephosphorylated in parallel with losses in ANP-dependent guanylyl cyclase activity (33). NPR-A isolated from resting 293 cells is phosphorylated on six residues (Ser-497, Thr-500, Ser-502, Ser-506, Ser-510, Thr-513) located within the glycine-rich elbow and putative ATP-binding region of its KHD (36). Replacement of any of these phosphorylated amino acids, but not residues flanking this region, with alanine
results in decreased ANP-dependent guanylyl cyclase activities (36). Receptors lacking four or more of these sites are completely unresponsive to hormone. NPR-B is also regulated by phosphorylation (37), and has five known phosphorylation sites within the amino-terminal portion of its KHD (Thr-513, Thr-516, Ser-518, Ser-523, Ser-526) (38). These data indicate that receptor phosphorylation is not merely modulatory, but is absolutely required for NP signal transduction. The NP receptor kinase has not been identified.

**Receptor Activation**

As a starting point for the molecular analysis of NP-dependent activation and desensitization of NPR-A, we have constructed a working model of this process (Fig. 2). In the absence of NP, the receptor exists as a homodimer or homotetramer. It is highly phosphorylated, and its guanylyl cyclase activity is tightly repressed. Upon NP binding, the oligomeric state of the receptor does not change (12,39) which indicates that receptor activation is not simply the result of ligand-dependent receptor oligomerization as is the case for many growth factor receptors. On the other hand, ANP binding does cause the extracellular juxtamembrane region of NPR-A to become susceptible to protease cleavage (18), which suggest that hormone binding induces a conformational change in this proline rich "hinge" portion of the receptor. Exactly how hormone binding transmits an activation signal across the membrane is unclear. However, since ATP is required for maximal NP-dependent activation and receptors lacking the KHD are constitutively active in the absence of ANP (40), one possibility is that hormone binding
facilitates ATP binding to the KHD. Once ATP is bound, a conformational change occurs within the KHD that facilitates three subsequent events. First, the normal inhibitory effect that the KHD has on catalytic activity is relieved and the guanylyl cyclase domains are allowed to come together to form two active sites per dimer. Two, an increased dissociation rate decreases the affinity of the extracellular domain of NPR-A for ANP. This effect also requires the KHD and is observed in whole cells as a time-dependent shift from high to low affinity ANP binding (41). Three, the conformational change in the KHD may expose the phosphorylated residues to a constitutively active, or perhaps a cGMP-activatable, protein phosphatase. In addition, the ATP-bound KHD may be a poorer substrate for the NPR-A kinase. The resulting dephosphorylated receptor is unresponsive to further hormonal stimulation.

In contrast to ATP, the diuretic drug amiloride stabilizes the high affinity binding state, and inhibits the hormone-dependent cyclase activity of NPR-A (41,42). Because high concentrations of amiloride inhibit the ATP-dependent activation of NPR-A, it has been suggested that ATP and amiloride compete for the same site (41). However, amiloride, but not the ATP, modulated the affinity of NPR-A for ANP in preparations that were subjected to limited trypsin proteolysis, suggesting that amiloride and ATP bind to different sites (24). The location of the ATP-binding site has not been determined, but it may reside within the NPR-A polypeptide because ATP analogs modestly activate guanylyl cyclase (43) and inhibit NP-binding activities (44) of highly purified receptor preparations. The $^{503}\text{GXGXXXG}^{509}$ sequence
within the KHD has been suggested to be the location of ATP interaction because of its similarity to the consensus ATP binding motif (GXGXXG) found in many protein kinases. In fact, this region has been dubbed the ATP regulatory domain or “ARM” by some investigators to emphasize its putative regulatory role (45). However, no direct ATP binding or cross-linking studies have been presented to support this hypothesis. These negative results are not unexpected because the EC₅₀ for ATP activation of NPR-A in guanylyl cyclase assays is approximately 0.1 mM (46). Hence, if this EC₅₀ is reflective of its binding constant for NPR-A, ATP may not bind tightly enough to obtain positive binding or cross-linking data. Regardless, this glycine motif is not required for ATP binding because the conversion of all three glycines to alanine has little or no effect on the activation of NPR-A (34). Other mutations within this region do decrease hormone-dependent activity, but they likely result from reductions in the phosphorylation state of the receptor (38).

**Homologous Desensitization**

Because synthetic BNP (Nesiritide) has proven to be clinically beneficial in the treatment of congestive heart failure (47), an understanding of the mechanisms involved in the desensitization of these receptors is important from a basic science and a clinical perspective. Hormone-dependent activities of NPR-A and NPR-B can be reduced by chronic exposure to NPs, known as homologous desensitization, or by exposure to agents other than NPs, referred to as heterologous desensitization. Homologous desensitization can be divided into processes that
are or are not mediated by receptor degradation, such as downregulation and dephosphorylation, respectively. Mechanistic analysis of the homologous desensitization of NPR-A and NPR-B has been hampered by the fact these receptors are often found in cells that also express NPR-C. Hence, losses in NP binding could theoretically result from the downregulation of the cyclase-linked receptors, NPR-C or both. In addition, because of the high affinity of these receptors for ligands, prebound NP can mask their ability to bind subsequent NP, a process known as prior receptor occupation (48). This phenomenon can lead to an under estimate of the amount of receptor present in cells and the erroneously conclusion that they are degraded when, in fact, their binding sites are masked.

One study that attempted to circumvent these potential pitfalls employed human embryonic kidney 293 cells that stably express NPR-A, but have no detectable NPR-B or NPR-C (33). Metabolically labeling of these cells with $^{32}$P-orthophosphate indicated that NPR-A is highly phosphorylated in the absence of NPs, and that ligand exposure results in a time-dependent dephosphorylation and desensitization of the receptor. The phosphorylation state of the receptor was tightly correlated with its hormone-dependent guanylyl cyclase activity. The decreased $^{32}$P signal was not explained by protein degradation because ANP exposure did not significantly reduce the amount of NPR-A purified from cells that were labeled with $^{35}$S-Met/Cys. In a separate study, tryptic phosphopeptide maps of overexpressed NPR-A from NIH-3T3 cells indicated that ANP exposure did not stimulate the dephosphorylation of a specific
phosphopeptide, although it clearly resulted in the dephosphorylation of the receptor (35). A similar scenario was reported for NPR-B (37). One explanation for these observations is that these cells contain two pools of receptors, one that is maximally phosphorylated and another that is completely dephosphorylated. Another possibility is that all phosphorylation sites are dephosphorylated to an equal extent.

Homologous desensitization of NPR-A has been observed in vitro as well. Foster and Garbers demonstrated that ATP-\(\gamma\)-S, but not the nonhydrolyzable ATP analog, AMPPNP, could sensitize NPR-A to subsequent stimulation by ANP and AMPPNP in crude membranes, an effect that presumably results from the limited ability of protein phosphatases to dephosphorylate thiophosphorylated substrates (49). They also found that the serine/threonine protein phosphatase inhibitor, microcystin, could prolong the maintenance of the initial rate of the reaction and increase the total amount of cGMP formed in guanylyl cyclase assays, again suggesting that dephosphorylation was sufficient for desensitization. To determine whether NPR-A was the target of the phosphatase, all six phosphorylation sites were mutated to glutamate to mimic a constitutively phosphorylated form of NPR-A (NPR-A-6E) (50). This receptor, but not one containing analogous alanine mutations, is stimulated ten-fold by ANP and ATP. In contrast to the wild-type receptor, NPR-A-6E is activated equally well by ATP and AMPPNP, and is completely unaffected by microcystin. These data suggest that the superior ability of ATP-\(\gamma\)-S and ATP to activate NPR-A results from their ability to serve as substrates in
a protein kinase reaction and that the protein that is being dephosphorylated in the in vitro cyclase assay is the receptor itself. Furthermore, NPR-A-6E, which cannot shed its negative charge via dephosphorylation, was shown to be resistant to homologous desensitization (50). These results indicate that NPR-A and NPR-B are homologously desensitized by receptor dephosphorylation, a unique paradigm compared to most G-protein coupled receptors that are desensitized by direct phosphorylation.

**Heterologous Desensitization**

The vasoconstrictory hormones arginine-vasopressin, angiotensin II and endothelin, which activate protein kinase C (PKC) through the stimulation of phospholipase Cβ, antagonize the actions of natriuretic peptides, and decrease both ANP- and CNP-dependent cGMP elevations in cultured cell lines (51-53). The reduced cGMP concentrations result from a calcium-dependent increase in phosphodiesterase activity (52,54) and a PKC-dependent decrease in guanylyl cyclase activity (35,52,55). Activation of PKC appears to be necessary and sufficient for the latter effect because phorbol 12-myristate 13-acetate (PMA), a direct activator of PKC mimics, and inhibitors of PKC block the ability of these hormones to desensitize natriuretic peptide receptors (35,52,55). The antagonism between these systems exists in the absence of strong PKC activators as well because the down-regulation of PKC by chronic exposure to PMA (56) or angiotensin II (48) results in the sensitization of NPR-A to ANP.
Hence, the activities of NPR-A and NPR-B are under the constant surveillance of the renin-angiotensin as well as other PKC activating systems.

Studies involving in vitro phosphorylation of NPR-A in crude membranes suggested that PKC directly phosphorylates NPR-A (57). However, interpretation of these observations is complicated by subsequent studies employing specific antibodies in which activation of PKC in whole cells resulted in the dephosphorylation, not phosphorylation of NPR-A (35). Unlike the global dephosphorylation associated with the homologous process, the heterologous desensitization is associated with the dephosphorylation of a single site or small subset of the total. Currently the identity of this site(s) within NPR-A is not known. PMA exposure results in the selective dephosphorylation of Ser-523 in NPR-B and reduces both basal and hormone-dependent cyclase activities (58). Importantly, replacement of this amino acid with alanine or glutamate abolished the inhibition, indicating that dephosphorylation of this single serine residue accounts for heterologous desensitization of NPR-B. Consistent with these data are results of Chrisman and Garbers showing that PDGF treatment of mouse fibroblasts results in the dephosphorylation and desensitization of NPR-B (59). Since this growth factor signals, in part, by activating PKC via phospholipase Cγ, dephosphorylation of Ser-523 may be instrumental in this process as well. Whether the PKC-dependent dephosphorylation of NPR-A and NPR-B results from the activation of a protein phosphatase or the inhibition of a protein kinase is not known, nor is the identity of the responsible protein kinase or phosphatase.
Finally, although both homologous and heterologous desensitization are mediated by dephosphorylation, several observations suggest that each pathway is unique. First, homologous, but not heterologous desensitization requires NP binding. Second, heterologous, but not homologous, desensitization requires PKC (35,55). Third, homologous desensitization involves global receptor dephosphorylation, whereas the heterologous process results in the loss of single phosphate (35). Lastly, the combined effect of ANP and PMA is greater than either alone, indicating that these processes are additive (35,55). Whether each process involves the same or a different protein kinase and phosphatase remains to be determined.

**Receptor Internalization and Degradation**

Early studies in PC12 cells indicated that both NPR-A and NPR-C internalize ANP (60). Once internalized, a portion of each receptor pool was recycled to the cell surface and another fraction was degraded (60). Unfortunately, because the cells in this study were not acid washed after exposure to ANP, the loss of ANP binding sites could be explained by receptor degradation or by prior receptor occupation (48). In Leydig cells, Pandey reported that NPR-A is readily internalized and that ANP degradation was markedly decreased when cells were incubated with NH₄Cl (61). In contrast, Koh and colleagues using lines of rat primary mesangial cells that exclusively or primarily express NPR-A, found that this receptor was constitutively membrane resident and was not internalized (62). In these cells, NH₄Cl had no effect on the residence time of ANP at the cell surface or on the appearance of ANP degradation products in the medium.
They did find a surprising increase in the off-rate of ANP from NPR-A when the temperature of the cells was raised from 30 to 37 °C. They concluded that NPR-A was not internalized nor was internalization needed to separate ligand from the receptor due to the very rapid dissociation rate that NPR-A has for NPs at physiologic temperature. Abe and coworkers observed a similar temperature-dependent binding interaction between NPR-A and an ANP analog in bovine lung membranes, and also concluded that internalization of NPR-A might not be needed to dissociate ANP and NPR-A (63). Using detergent-dependent guanylyl cyclase assays and Western blot analysis, we found that addition of ANP to 293 cells expressing NPR-A resulted in receptor degradation, although this process was slow with a $t_{1/2}$ of approximately 4h (50). Currently, the roles of internalization and degradation in the regulation of NPR-A are unclear, although these data could be explained if this process is a cell-type-specific phenomenon. In contrast, virtually nothing is known about the internalization and degradation of NPR-B.

Conclusions and Perspectives

Over the past fifteen years much has been learned about the location, structure and physiologic function of NPR-A and NPR-B (4-6). Furthermore, it has become clear that the majority, but perhaps not all, of the known effects of NPs are mediated through the production of cGMP. Surprisingly, in comparison to other signaling pathways, very little information has been published on the cellular regulation of these receptors. It is particularly remarkable that despite the development of sensitive techniques like two-hybrid screens and glutathione-S-transferase
fusion protein "pull down" assays that measure protein-protein interactions, few proteins have been shown to associate with these receptors (64,65). The significance, if any, of the interactions that have been identified remains to be determined. Is NP signaling that different from other transduction pathways? Even within the particulate guanylyl cyclase family, it is now well established that small calcium-binding proteins interact with the cytoplasmic domain of retinal members of this family. Within the next few years it is likely that a number of molecules will be discovered that regulate NP receptors as well. Clearly the NP receptor kinase and phosphatase are prime candidates for identification. Since phosphorylation is obligatory for the activation of NPR-A and NPR-B, loss of function mutations within the enzyme(s) that mediates this process may yield phenotypes similar to those of animals lacking NPs. Hence, it is possible that some forms of idiopathic hypertension or dwarfism may be explained by mutations in the NP receptor kinase. Likewise, activating mutations within the NP receptor phosphatase may result in these diseases. Finally, with the success of BNP in the treatment of congestive heart failure and the vasopeptidase inhibitor, Omapatrilat which works in part by increasing the concentrations of NPs, as an antihypertensive agent, the clinical potential of this pathway is evident. The identification of proteins that regulate this pathway will likely provide additional drug targets for the treatment of these and other diseases.

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Figure 1. Model of the structures and functions of natriuretic peptides and their receptors. See text for description. Numbering is for rat sequences. Drawings are not to scale.

Figure 2. Hypothetical model of the activation and homologous desensitization of NPR-A. See text for description.

References
Natriuretic Peptide

Receptor

Ligand Binding Domain

Membrane

Kinase Homology Domain

Hinge Region

Guanylyl Cyclase Domain

Physiologic Response

Natriuretic Peptide

NPR-C

NPR-A (GC-A)

NPR-B (GC-B)

GTP → cGMP

NP degradation
cAMP ?
cGMP ?

vasorelaxation

diuresis, natriuresis
renin, aldosterone

vasorelaxation

cell proliferation

long bone growth

vasorelaxation

diuresis, natriuresis
renin, aldosterone

vasorelaxation

cell proliferation

long bone growth

vasorelaxation

diuresis, natriuresis
renin, aldosterone

vasorelaxation

cell proliferation

long bone growth

vasorelaxation

diuresis, natriuresis
renin, aldosterone

vasorelaxation

cell proliferation

long bone growth

vasorelaxation

diuresis, natriuresis
renin, aldosterone

vasorelaxation

cell proliferation

long bone growth

vasorelaxation

diuresis, natriuresis
renin, aldosterone

vasorelaxation

cell proliferation

long bone growth
Desensitized

Hormone bound

Active

Basal

Kinase + ATP

Natriuretic Peptide

ATP

P-tase

cGMP

GTP

ATP

ATP

P

cGMP

GTP

NP