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REVIEW

Natriuretic Peptides and Their Receptors

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BACKGROUND

In 1956, Kisch examined the guinea pig heart under the electron microscope and found atrial granules that were very similar to the storage granules seen in the hormone-secreting cells of the pancreas and the anterior pituitary gland [55]. In 1981, de Bold and his colleagues identified atrial natriuretic peptide (ANP) as an endogenous diuretic that is stored in atrial granules [22]. This discovery opened up a new field in cardiovascular research. Subsequently, brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) were isolated from extracts of porcine brain [105, 106]. Members of the family of natriuretic peptides were also found in various non-mammalian species. Two distinct types of receptor for such peptides have been identified by molecular cloning studies [15, 17, 31, 70, 101]. One type of receptors includes the type A natriuretic peptide receptor (NPR-A or GC-A) and the type B natriuretic peptide receptor (NPR-B or GC-B). These receptors are members of the receptor guanylate cyclase family and are capable of synthesizing their own second messenger, cGMP. The other type of receptor includes the type C natriuretic peptide receptor (NPR-C) which has almost no intracellular domain. Much is known about the biochemistry and physiology of these receptors in mammalian species. Natriuretic peptide and receptor system in mammals are summarized in Table 1. However, little information has been reported about receptors for natriuretic peptides in non-mammalian species. Therefore, we cloned NPR-B and NPR-C from an eel gill cDNA library and performed structural analysis of the encoded proteins [52, 110].

ANP plays an important role in the regulation of body

fluid volume, electrolyte balance and blood pressure by causing diuresis, natriuresis, and vasorelaxation. These biological activities of natriuretic peptides are thought to be mediated by the intracellular accumulation of cGMP as a consequence of the activation of receptor guanylate cyclases. Located not only in the kidney, adrenal gland, and vasculature, natriuretic peptide receptors are present in a variety of other tissues and organs, namely, heart, lung, neurons, endocrine organs, cartilage, and bone. Such a wide distribution suggests that natriuretic peptides might be multifunctional peptides.

Since the discovery of ANP, an avalanche of published reports has described numerous members of the family of natriuretic peptides and their receptors. Several reviews already provide excellent and detailed summaries of the chemistry, physiology, and molecular biology of the natriuretic peptides and their receptor systems [4, 10, 27, 34, 43, 59, 98, 125]. In this article, after a brief description of the biochemistry of natriuretic peptides and their receptors, we shall focus on differences in the structural aspects of receptors for natriuretic peptides between mammalian and non-mammalian species.

I Natriuretic peptides

1. Overview

ANP was the first reported member of the large family of natriuretic peptide hormones and it is present at high concentrations in the atrial tissue of many species. The ventricle also produces ANP, albeit at levels 1,000-fold lower than the atrium. ANPs have been found in a wide range of tissues

TABLE 1. Natriuretic peptide and receptor system in mammals

Ligand	Source	Receptor	Target Organ	Effects
ANP	atrium	NPR-A & -C	adrenal gland, kidney, vasculature	aldosterone ↓, natriuresis, diuresis, vasodilation
BNP	atrium, ventricle	NPR-A & -C	same as above	same as above
CNP	brain, endothelium, cartilage	NPR-B & -C	brain, vasculature, cartilage	neuromodulation, proliferation ↓

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where they may have a variety of functions. BNP and CNP were isolated from extracts of porcine brain by Sudoh *et al.* [105, 106]. In mammals, ANP, BNP, and CNP have been found in various animals, such as the human, bovine, pig, and rat. In non-mammalian species, ANP has been isolated from two species of frogs (*Rana catesbeiana* and *R. ridibunda*) and eel (*Anguilla japonica*), BNP from fowl (*Gallus domesticus*), and CNP from fowl, bullfrog, newt (*Cynopus pyrogaster*), killifish (*Fundulus heteroclitus*), eel, and four species of sharks (*Scyliorhinus canucula*, *Squalus acanthias*, *Triakis scyllia*, and *Lamna ditropis*). Furthermore, it has been reported that a peptide toxin (DNP) isolated from the venom of the green mamba (*Dendroaspis angusticeps*) and ventricular natriuretic peptide (VNP) isolated from eel and trout (*Oncorhynchus mykiss*) exhibit sequence homology to and share bioactivity with natriuretic peptides. cDNA of eel ANP and VNP [117] and dogfish CNP [100] have been

isolated.

The structures of 23 members of the natriuretic peptide family are shown in Figure 1. The amino acid sequences of ANPs and CNPs are highly conserved across species but those of BNP vary. In particular, human, porcine, and rat CNPs are identical. CNPs from the fowl and bullfrog are identical to the mammalian form with the exception of three amino acid substitutions. Furthermore, homology of greater than 80% has been noted between mammalian and fish CNPs despite the large phylogenetic distance between mammals and fish. By contrast, mammalian BNPs are only 50% homologous to one another at the amino acid level. It remains to be determined whether this variation among species in BNP is meaningful.

ANP, like many other biologically active peptides, is synthesized first in a "prepro" form that contains from 149 to 153 amino acids, depending upon the species. Prepro ANP

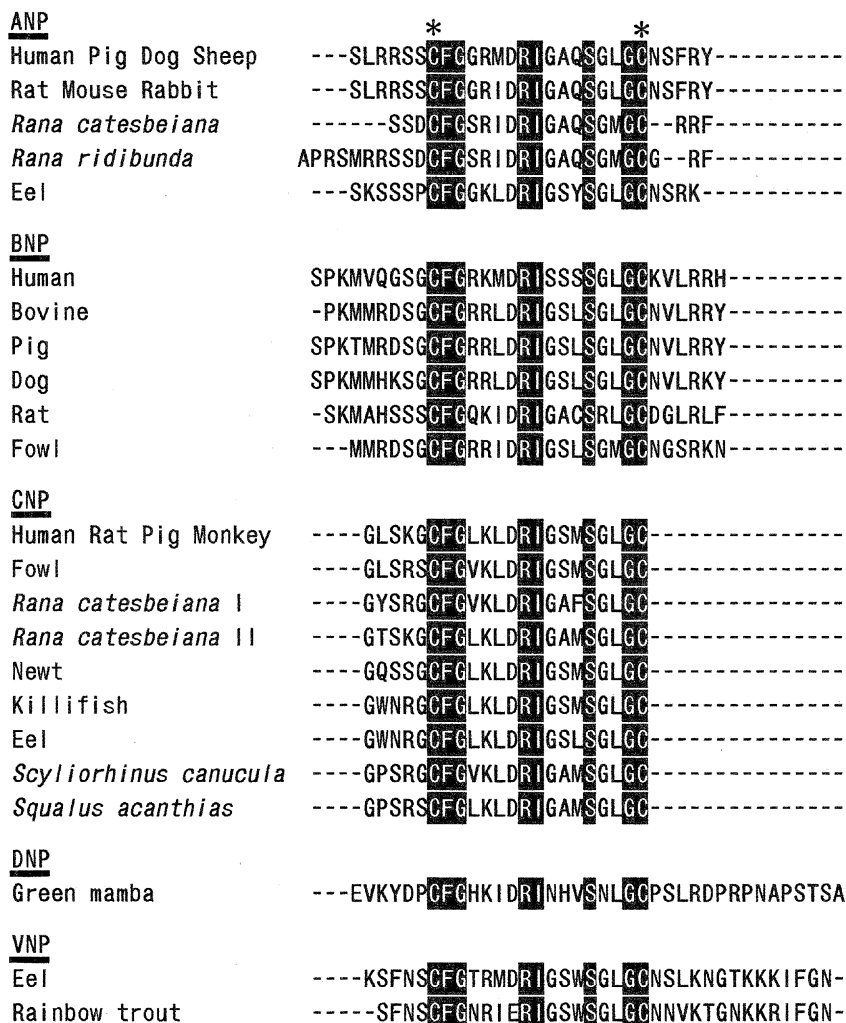


Fig. 1. Comparison of the amino acid sequences of natriuretic peptides from various classes of vertebrate. Previously published sequences for A-type natriuretic peptides of human [49], rat [30], *Rana catesbeiana* [96], *Rana ridibunda* [63] and eel [113]; B-type natriuretic peptide of human [80], bovine [81], pig [105], dog [30], rat [56], and fowl [1, 75]; C-type natriuretic peptides of human [120], fowl [8], *Rana catesbeiana* I [127], *Rana catesbeiana* II [58], newt [79], killifish [90], eel [115], *Scyliorhinus canucula* [109], and *Squalus acanthias* [100]; the natriuretic peptide of the green mamba [102], and the ventricular natriuretic peptide of eel [114] and rainbow trout [116] are shown in the single-letter amino acid code. Gaps have been introduced to maximize matching. Black boxes enclose identical amino acids. *Disulfide linkages between these cysteine residues are conserved in all the natriuretic peptides.

is rapidly converted to a 126-amino-acid peptide, proANP, the predominant storage form of ANP. The bioactive peptide is generated by proteolytic cleavage of proANP just prior to the release of ANP into the circulation by an increase in blood volume. BNP [89] and CNP [57, 119] are also synthesized as large precursors. The half-life of ANP in the circulation is very short; in humans, the half-life of ANP in plasma has been estimated to be about 3 minutes [126]. ANP is metabolized by a neutral endopeptidase [54] and is trapped from the circulation after its binding to NPR-C [71].

2. Structure

The natriuretic peptides form a family of structurally related peptides, as shown in Figure 1. These peptides have in common a ring of 17 amino acids that is formed via a bow between two cysteine residues and they exist as multiple amino- and carboxyl-terminally extended or truncated forms. Figure 2 shows the mature forms of the human peptides; 11 of the amino acids are identical in ANP, BNP, and CNP. BNP-32 is the major form of the hormone in human atrial tissue, and human plasma has been reported to contain both BNP-32 and a high-molecular-weight form of BNP (probably

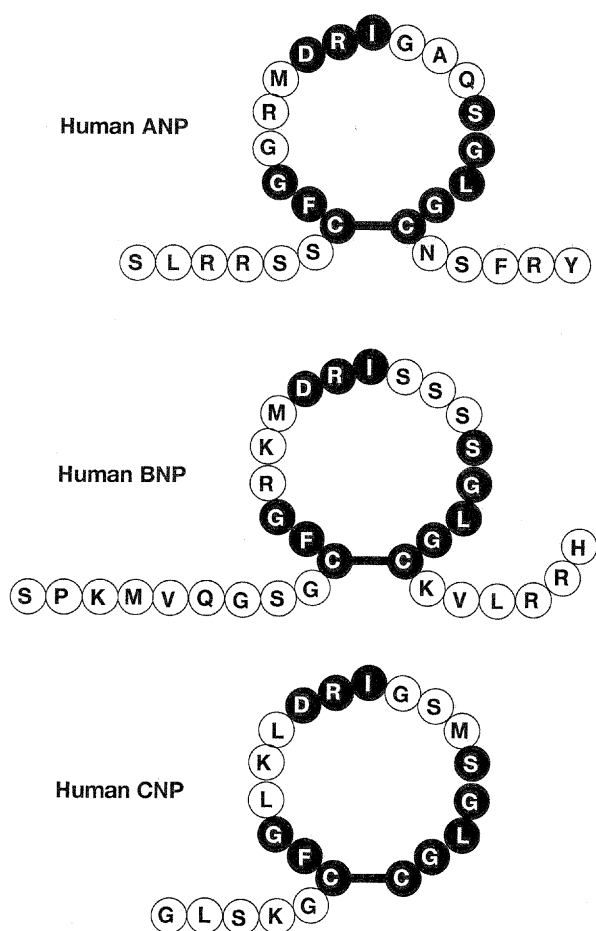


FIG. 2. Structures of the three major subtypes of natriuretic peptides. Filled circles show amino acids that are identical in the three members of the family of human natriuretic peptides.

pro-BNP). Two forms of CNP are present in most tissues that express CNP; CNP-53 [74, 119] is identical to CNP-22 except for an extension of 31 amino acids at the amino-terminal end. Urodilatin, first isolated from human urine and synthesized in the kidney, is identical to ANP except for the addition of four amino acids at the amino-terminal end [93].

3. Biological action

ANP elicits a variety of responses that are directed toward the reduction of both blood pressure and blood volume. In the kidney, ANP has powerful natriuretic effects that result from the direct inhibition of the absorption of sodium ion in the collecting ducts, increased glomerular filtration, and the modulation of renal vascular resistance [23, 128]. Injection of ANP into the rat brain causes changes in diuresis and salt appetite [29, 45], in heart rate and blood pressure [66, 104], and in the secretion of vasopressin from the hypothalamus [97]. ANP also lowers vascular tone that has been induced by various vasoconstrictors. Furthermore, ANP inhibits the secretion of aldosterone from the adrenal gland, the release of vasopressin from the posterior pituitary and the secretion of renin from the kidney [10, 21, 37]. A number of reports on the physiologic effects of ANP have been published. By contrast, the major roles of BNP and CNP remain to be elucidated.

As its name suggests, BNP was originally identified in porcine brain, but studies in the rat [80], pig [73], and human [118] have demonstrated that levels of BNP in the heart are much higher than those in the brain. Resembling ANP, BNP can elicit vasorelaxing, natriuretic, and diuretic responses. It is of particular interest, moreover, that expression and release of BNP from the ventricle increase dramatically in patients with severe congestive heart failure [78].

In mammals, CNP has been detected at very low levels within the circulation. CNP was first identified in porcine brain [106] and its high concentrations in the brain and the central nervous system [57, 61] suggest that CNP acts as a neuropeptide. CNP has also been detected in endothelial cells [108], monocytic cells [44], and chondrocytes [40], suggesting an autocrine/paracrine role for CNP in the regulation of vascular tone, growth, or hormone release. However, the precise functional role of CNP has not yet been elucidated.

In non-mammalian vertebrates, a spectrum of actions of natriuretic peptides involve the cardiovascular system, renal and extrarenal osmoregulatory mechanisms, and the central nervous system [28, 112]. Mammalian as well as homologous ANP are vasodepressor in birds [39] and fish [64, 113] except a transient pressor effect observed in the trout which is mediated by sympathetic activation [84]. Eel ANP inhibits drinking in esophagus cannulated eels in a dose-dependent manner [111]. Mammalian or homologous ANP also inhibits the absorption of Na⁺ ion and water across the intestine of the flounder [82] and eel [5]. ANP inhibits

aldosterone secretion in the fowl [38], turtle (*Amyda japonica*) [19], and frog (*Rana ridibunda*) [67] as in mammals, but it stimulates cortisol secretion in seawater fish [9]. Teleost fish utilize cortisol as mineralocorticoid. Mammalian ANP is diuretic and natriuretic in the fowl [39] and teleost fish [64, 84], but it is rather antidiuretic in the eel when homologous ANP is administered [111]. Antidiuretic effect of ANP is also reported in a shark, *Squalus acanthias* [11].

It was, recently, proposed that natriuretic peptides have growth-regulatory properties in a variety of tissues and cultured cells, such as adrenal gland, kidney, brain, bone, smooth muscle cells, and endothelial cells [7, 65]. For example, Levin has reviewed the relationship between NPR-C and the proliferation of cells [65]. Appel [6] and Itoh *et al.* [46] have described how ANP inhibits mitogenesis of rat mesangial cells and vascular smooth muscle cells, respectively, via the cGMP that is produced by the receptor guanylate cyclase. Furthermore, Pines and Hurwitz [87] showed that the proliferation of chondroprogenitor cells of the avian epiphyseal growth plate is modulated by ANP. This modulation is also probably mediated by cGMP as a second messenger. We have also reported that CNP inhibits the proliferation of rat chondrocytes in an autocrine/paracrine manner [40]. Recent studies by Garg and Hassid support the concept that cGMP is important in the inhibition of mitogenesis in rat mesangial cells [35] and vascular smooth muscle cells [36]. However, the cellular mechanisms involved in these actions of natriuretic peptides are by no means totally understood.

II Receptors for natriuretic peptides

1. Overview

Receptors for natriuretic peptides can be biochemically and functionally divided into two major classes. The NPR-A (GC-A) and NPR-B (GC-B) receptors are members of the receptor guanylate cyclase family and each seems to be present as a tetramer, formed via disulfide bonds, on the plasma membrane [18, 48, 68]. The other type of receptor contains NPR-C which has a single membrane-spanning domain and a very short cytoplasmic tail (37 amino acids). NPR-C exists as a homodimer [103]. The structures of three representatives of the family of natriuretic peptide receptors are illustrated schematically in Figure 3. Yamaguchi *et al.* [124] characterized the gene for rat NPR-A (17.5 kilobases) and we [94] characterized the gene for bovine NPR-C (>85 kilobases). These genes are very similar in terms of the organization of exons and introns that correspond to the extracellular domain and the membrane-spanning domain. It appears, therefore, that the genes for NPR-A and NPR-C arose from several common ancestral genes by shuffling of exons.

Figure 4 shows a comparison of the amino acid sequence of the extracellular and membrane-spanning domains of natriuretic peptide receptors published to date. Natriuretic

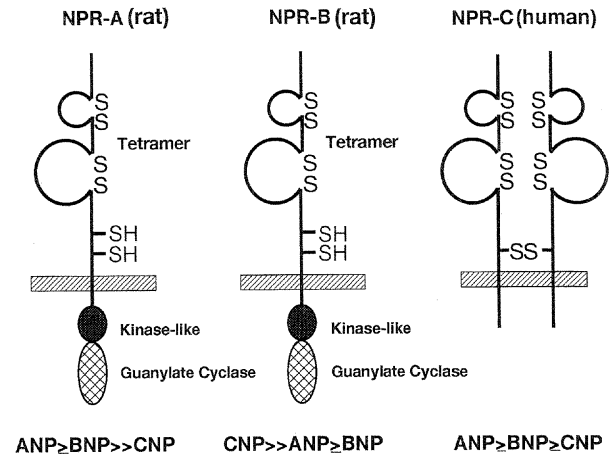


FIG. 3. Structures and properties of members of the family of receptors for natriuretic peptides. Disulfide bonding patterns and domain structures of rat NPR-A [17] and NPR-B [101] and human NPR-C [88] are shown schematically.

peptide receptors have been isolated from many mammalian species but their genes have not been cloned from non-mammalian species. As shown in Figure 4, the amino acid sequences of the extracellular domains that contain the ligand-binding sites are not highly conserved among the three receptors. However, using site-directed mutagenesis, we determined that His-Trp residues, which are highly conserved, contribute significantly to the binding of ligands to the receptors [47].

2. Membrane-bound guanylate cyclases (NPR-A and NPR-B)

NPR-A was initially cloned from rat brain [70] and human kidney [17] by use of a cDNA that encoded the membrane form of guanylate cyclase from the sea urchin *Arbacia punctulata* by Garbers and his colleagues. After the discovery of NPR-A, low-stringency hybridization resulted in the discovery of a second form of receptor guanylate cyclase, NPR-B [15, 101]. NPR-A and NPR-B each has a single membrane-spanning domain and large extracellular and cytoplasmic domains. In addition to the guanylate cyclase domain, the cytoplasmic tail contains a protein kinase-like domain that acts as a modulator of the activation of guanylate cyclase [16] (Fig. 3). Ohyama *et al.* [83] demonstrated the presence of an alternative splicing variant of rat NPR-B that lacks a part of the cytoplasmic regulatory domain encoded by exon 9 and also lacks some biological functions. NPR-A and NPR-B are structurally and functionally very similar but they have quite different ligand specificities; NPR-A responds to ANP and BNP, whereas NPR-B is highly specific for CNP [60]. A selective nonpeptide antagonist, HS-142-1, that is specific for NPR-A and -B has been reported but its mechanism of action is unclear [77]. HS-142-1 abolishes ANP-induced diuresis and natriuresis in animals.

We have reported marked increase in levels of cGMP

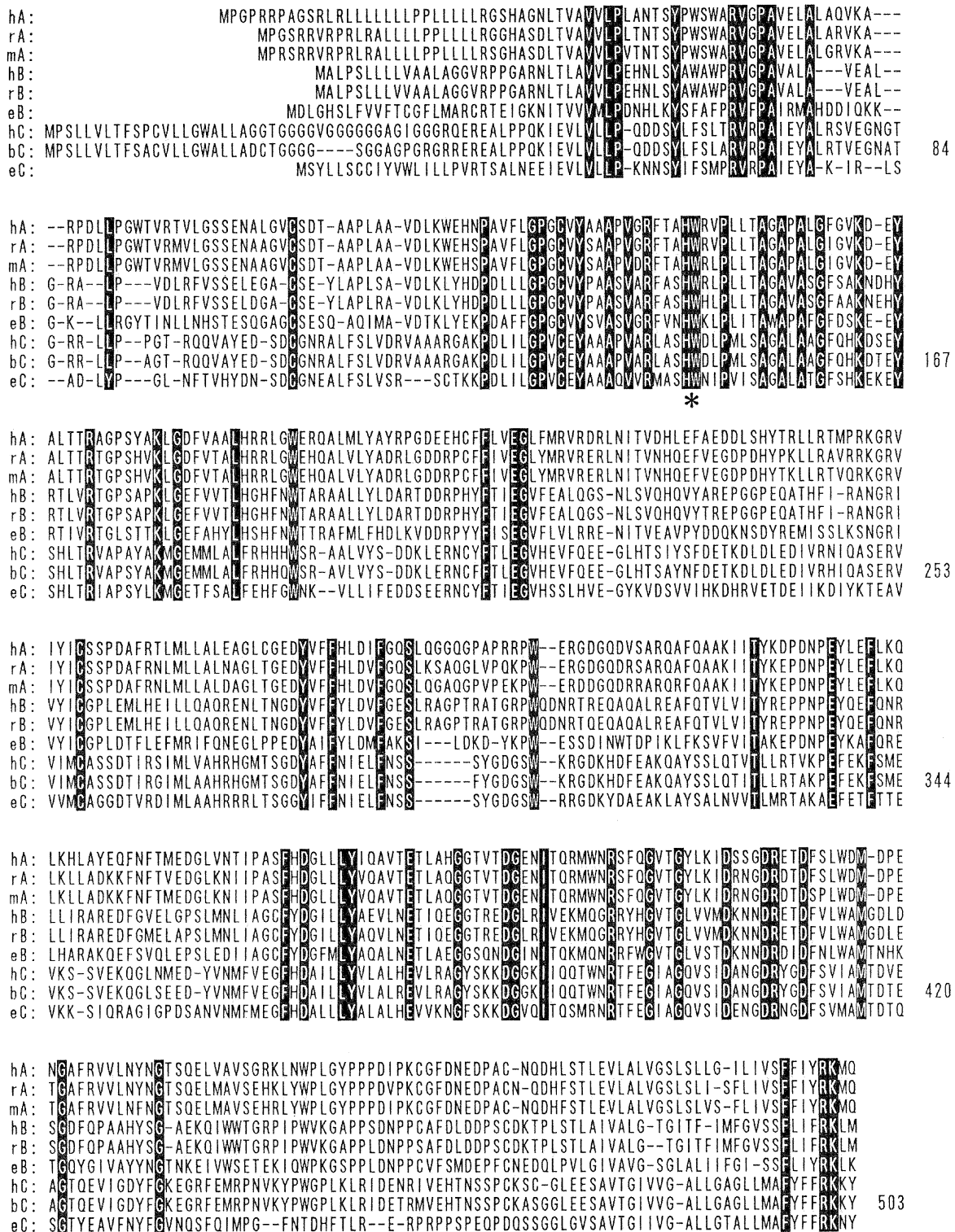


Fig. 4. Sequence comparison of the extracellular and membrane-spanning domains of receptors for natriuretic peptides. Previously published sequences for human NPR-A (hA) [70], rat NPR-A (rA) [17], mouse NPR-A (mA) [86], human NPR-B (hB) [15], rat NPR-B (rB) [101], eel NPR-B (eB) [52], human NPR-C (hC) [88], and bovine NPR-C (bC) [31], and the sequence of eel NPR-C (eC) [110] are shown in the single-letter amino acid code (only the extracellular and membrane-spanning domains are shown in the sequences of NPR-A and NPR-B). Gaps have been inserted to achieve maximum similarity. Black boxes enclose identical amino acids. Underlining shows regions of putative membrane-spanning domains. An asterisk shows the HW residues that contribute to binding of the ligand. The numbers on the right are the numbers of the last amino acids on the respective lines, counted from the first amino acid of the sequence of bovine NPR-C (bC), which was taken as number 1.

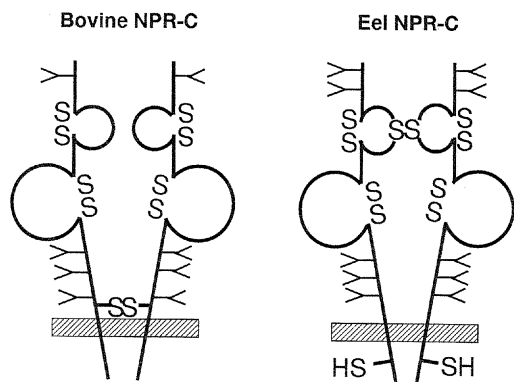


FIG. 5. Comparison of the disulfide bonding patterns of bovine and eel receptors for C-type natriuretic peptide. Y indicates potential sites of *N*-glycosylation. The interchain disulfide bonding responsible for the formation of covalently linked homodimers is completely different between bovine NPR-C [31] and eel NPR-C [110].

mediated by the NPR-A and -B and a decrease in the expression of NPR-C in cultured vascular endothelial cells treated with NaCl [51] or exposed to high pH (pH 7.7) [50]. Kato *et al.* [53] also showed that cGMP down-regulates NPR-C in cultured vascular endothelial cells. Hirata *et al.* [42] demonstrated the ligand-induced and phorbol ester-induced down-regulation of NPRs. Chabrier *et al.* [14] demonstrated the induction by angiotensin II of down-regulation of NPRs in rat vascular smooth muscle cells.

NPR-A is formed mainly in the kidney, adrenal gland, lung, and vascular bed. The diverse biological activities of ANP are thought to be mediated by the intracellular accumulation of cGMP that is produced by NPR-A.

Autoradiographic studies with $^{125}\text{I}[\text{Tyr}^0]\text{-CNP}$ [62], Northern blot analysis [20, 101], PCR analysis [13, 83] and *in situ* hybridization [123] have demonstrated the existence of NPR-B in many tissues of the mammalian body, including the brain, lung, kidney, adrenal gland, intestine, uterus, and oviduct. NPR-B has also been identified in cultured cells, such as rat vascular smooth muscle cells [32], brain endothelial cells [122], glioma cells [26], pheochromocytoma (PC12) cells [92], chondrocytes [40, 41] and human mesangial cells [107]. However, the physiological roles of NPR-B in the target tissues have not yet been elucidated.

Recent studies have suggested a role for the CNP/NPR-B system in specific tissues and cells. For example, porcine seminal plasma contains large amounts of CNP, and NPR-B mRNA has been demonstrated in the uterus and oviduct, suggesting that the CNP/NPR-B system might play a role in fertilization [20]. This system also has been reported as a potent inhibitory regulator of cell proliferation [33, 40]. In the pituitary, CNP is an autocrine regulator of gonadotropes [72]. NPR-B has been cloned from the human retina, and ATP has been shown to be a prerequisite for CNP signaling in the retina [24].

3. C-Type natriuretic peptide receptor (NPR-C)

NPR-C has been purified from bovine lung [103] and cultured rat smooth muscle cells [99]. Molecular cloning has shown that NPR-C lacks a kinase-like domain and a guanylate cyclase domain [31]. We demonstrated the presence of a variant of NPR-C, produced by alternative splicing of RNA, that has an additional cysteine residue between the sixth intron and seventh exon [76]. Binding studies have demonstrated that NPR-C has equal affinity for each of the three types of natriuretic peptide. A specific competitor of NPR-C, designated C-ANF, with the structure des [Gln¹⁸, Ser¹⁹, Gly²⁰, Leu²¹, Gly²²]ANP₄₋₂₃-NH₂, has been synthesized [71]. Although NPR-C accounts for most of the NPR in most target tissues (more than 95% of the total population of NPRs), its physiological roles are not entirely clear. Maack and his colleagues [71] postulated that this protein functions as a clearance receptor to remove ANP from the circulation. However, recent evidence suggests that NPR-C inhibits the adenylate cyclase/cyclic AMP system through activation of a pertussis toxin-sensitive Gi protein in some tissues [2, 3]. Tseng *et al.* [121] showed that ANP inhibits formation of cAMP and secretion of thyroglobulin in cultured human thyroid cells which only have NPR-C. Antimitogenic and antiproliferative effects of ANP, mediated by NPR-C, have been proposed in rat astroglial cells [69], rat aortic smooth muscle cells [12], and hepatoblastoma cells [91]. In these cells, the NPR-C-selective ligand C-ANF inhibited the proliferation of cells in a cGMP-independent manner.

III Receptors for natriuretic peptide in eel

Natriuretic peptide receptors of non-mammalian species have not yet been purified, cloned, and characterized. However, the physiological studies of Olson and Duff suggested the presence of receptors for natriuretic peptides in fish tissues such as gill, kidney, heart, and the vascular bed [25, 84, 85]. We recently found the dense distribution of natriuretic peptide receptors in eel gill by autoradiographic studies and a binding assay with ^{125}I -labeled eel ANP or VNP [95]. Subsequently, we cloned NPR-B [52] and NPR-C [110] from an eel gill cDNA library and performed a comparative study of NPR-B or NPR-C by expressing the cDNAs in COS-1 cells. We chose the eel for our studies since eels are euryhaline and three types of homologous natriuretic peptide (ANP, CNP, and VNP) have been isolated [113-115]. Euryhaline fish appear to be attractive species for studies of the physiology of the natriuretic peptide system since they migrate between fresh water and salt water. Analysis of their natriuretic peptide systems is expected to reveal valuable information about the roles of the system in osmoregulation.

Eel NPR-B has, like mammalian NPR-B, a specific CNP-induced guanylate cyclase activity. Sequence comparisons between the eel mammalian receptors demonstrate a relatively low degree of similarity (~44%) in the extracellu-

lar domain, as compared to very high similarity (~84%) in the cytoplasmic domain. RNase protection analysis of the mRNA for eel NPR-B revealed that the message is expressed predominantly in the gill, liver, and atrium.

Eel NPR-C has a disulfide-linked homodimeric structure, as does mammalian NPR-C. The deduced amino acid sequence of eel NPR-C is about 60% homologous to that of mammalian NPR-C. Figure 5 shows a comparison of disulfide bonding patterns between eel and bovine receptors for C-type natriuretic peptides. Site-directed mutagenesis revealed that eel and mammalian NPR-C are quite different in their interchain disulfide-bonding pattern. In eel, the second Cys residue in the first disulfide-linked loop is involved, while in mammals it is the fifth Cys residue that is involved in the covalent dimerization. In spite of the difference in disulfide bonding patterns, eel NPR-C has almost identical affinity for each of the three ligands, which is a typical characteristic of NPR-C. The eel receptor is also different from the mammalian NPR-C in the number of sites of *N*-glycosylation. NPR-C is expressed in high levels in the gill, atrium, and ventricle. The levels of NPR-C mRNA were found to be down-regulated in most tissues when eels were transferred from fresh water to seawater. However, in the anterior intestine, the levels were up-regulated.

The above results for eel natriuretic peptide receptors suggest that NPR-B and NPR-C play an important role in the adaptation to changes in salinity in the euryhaline eel.

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