

Aleksandra Sindić<sup>1,\*</sup>,  
Marina Dobrivojević<sup>2</sup>,  
Jochen R. Hirsch<sup>3</sup>

<sup>1</sup>Department of Physiology,  
Croatian Institute for Brain Research,  
School of Medicine, University of Zagreb,

<sup>2</sup>Department of Histology,  
Croatian Institute for Brain Research,  
School of Medicine, University of Zagreb,

<sup>3</sup>Pharis Biotec GmbH and CardioPep  
Pharma GmbH, Feodor-Lynen-Str. 31,  
D-30625 Hannover, Germany

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# NATRIURETIC PEPTIDES IN BRAIN PHYSIOLOGY

## Abstract

Natriuretic peptides (NPs) regulate salt and water homeostasis by inducing natriuresis and diuresis in the kidney. These actions in addition to those via the heart and vascular system play important roles in the regulation of blood pressure. In the central nervous system NPs play a significant role in neuronal development, synaptic transmission and neuroprotection. Currently, six different human NPs have been described: atrial natriuretic peptide (ANP), urodilatin (URO, renal natriuretic peptide), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) as well as guanylin and uroguanylin. ANP, URO and BNP activate the natriuretic peptide receptor A (NPR-A or guanylate cyclase A (GC-A)) while CNP activates natriuretic peptide receptor B (NPR-B or guanylate cyclase B (GC-B)). Guanylin and uroguanylin are known to activate guanylate cyclase C (GC-C). The receptors GC-A, GC-B, and GC-C are widely expressed in the human body. Currently, GC-B and CNP seems to have the highest expression in central nervous system compared to other NPs and their receptors. All known NPs generate intracellular cyclic GMP (cGMP) by activating their specific guanylate cyclase receptors. Subsequently, cGMP is able to activate protein kinase I or II (PKG I or II) and/or directly regulate transmembrane proteins such as ion channels, transporters and pumps. NPs also bind to the natriuretic peptide receptor C (also called clearance receptor NPR-C) which is a major pathway for the degradation of NPs and has no guanylate cyclase activity. In this review we will focus on new insights regarding the physiological effects of NPs in the brain, especially specific areas of their signaling pathways in neurons and glial cells.

## Keywords

• Neurons • Glia • Plasticity • Natriuretic peptides • cGMP

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## 1. Introduction

Natriuretic peptides (NPs) induce natriuresis and diuresis in the kidney and cause vasodilatation of the blood vessels and therefore are involved in blood pressure regulation [1]. Six different NPs have been identified: atrial natriuretic peptide (ANP), urodilatin (URO) as the kidney isoform of ANP, brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) as well as the intestinal natriuretic peptides guanylin and uroguanylin. They all share a similar peptide structure. A functionally important structural feature of ANP, URO, BNP and CNP is the ring structure formed by a disulfide bridge between two cysteine residues (see Figure 1).

### 1.1 Natriuretic peptides and their function

ANP is currently the most extensively investigated natriuretic peptide. Regulation of ANP synthesis in the heart atrium is

directly dependent on volume expansion, hypoxia, [2-4], decrease of intracellular pH, increased heart rate, atrial stretch, sympathetic stimuli and metabolic factors [5-7]. In the kidneys, ANP affects sodium (Na<sup>+</sup>) and water reabsorption along the nephron by inhibiting various transport systems such as Na<sup>+</sup>/H<sup>+</sup>-antiporter [8], Na<sup>+</sup>/K<sup>+</sup>-ATPase [9,10], Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup>-cotransporter [11], non-selective cation channels [12], and aquaporins (AQP) (via inhibition of the antidiuretic hormone ADH) [13]. ANP mostly works as an opponent to the renin angiotensin aldosterone system (RAAS) by inhibiting renin secretion [14]. In addition to the mentioned actions of ANP, it is also found to decrease salt appetite and the production of ADH in the hypothalamus when injected into the ventricular system of the brain [15,16]. Furthermore, it decreases sympathetic activity and lowers baroreceptor responses to high blood pressure [17-20].

Although BNP was discovered in the brain and named accordingly, it is actually produced in the heart and its major function lies in the regulation of the cardiovascular system. ANP and BNP can also be used as markers for Alzheimer's disease as well as stroke and are possibly involved in the pathophysiological mechanisms of these diseases [21-25]. It has been known that during ischemic stroke ANP increases permeability of brain capillaries and its expression is increased in glial cells surrounding the ischemic core [26-28]. Even though NPs were shown to increase capillary permeability in ischemic stroke and intracranial hemorrhage, ANP is able to reduce the size of brain areas affected with edema in those conditions [29,30]. The beneficial effects of ANP on developing brain edema could be due to inhibition of immune system cells and microglia as recently suggested [31] and by inhibition of mediators of inflammation activated by injury (unpublished results from our group).

\* E-mail: asindic@mef.hr

CNP is mainly expressed in the central nervous system, bone and vasculature. In hypothalamus CNP expression is 50 times higher compared to ANP and BNP [32,33]. In a similar but more potent way than ANP, CNP, when applied intracranially, inhibits the production of ADH by inhibiting the L-type  $\text{Ca}^{2+}$ -channels [34-37].

## 1.2 Receptors and signaling pathways of natriuretic peptides

The intracellular concentration of cyclic GMP (cGMP - the primary second messenger for NPs) is elevated by activation of different guanylate cyclase receptors. cGMP activates guanylate cyclase receptors. cGMP activates cGMP-dependent protein kinase I (PKG I) or II (PKG II) as well as cGMP gated ion channels [38,39]. cGMP via activation of different cGMP dependent phosphodiesterases (PDE2, PDE3 and PDE5) which degrade cAMP, influence the intracellular cAMP concentration and it's signaling cascade [39] (Figure 2).

The growing family of guanylate cyclases includes soluble cytoplasmatic guanylate cyclase which is a receptor for nitric oxide (NO) and carbon monoxide (CO) [40] as well as 7 types of transmembrane guanylate cyclases. Natriuretic peptide receptor A (NPR-A) known as guanylate cyclase A (GC-A), natriuretic peptide receptor B (NPR-B or GC-B), and guanylate cyclase C (GC-C) are receptors for known natriuretic peptides and are involved in the regulation of salt, water and blood pressure homeostasis. GC-A is the receptor for ANP, BNP and urodilatin while GC-B is the receptor for CNP. GC-C is bound by guanylin, uroguanylin and heat-stable enterotoxin of *E. coli* (STa) (Figure 3).

All NPs and their receptors can be found in the brain. Expression of NPs and their receptors is given in Table 1. mRNA for GC-A is located in the glial cells as well as in neurons of the forebrain [41,42]. Even though NPR-B (GC-B) and it's binding hormone CNP are the most abundant in the brain (Table 1) it's truncated form, NPR-Bi shows a much stronger expression signal in the brain [43-45]. NPR-Bi acts as tyrosine kinase and not as guanylate cyclase, however it's specific function is still unknown. GC-C is the receptor for the intestinal natriuretic peptides guanylin and uroguanylin and it's mRNA is expressed in

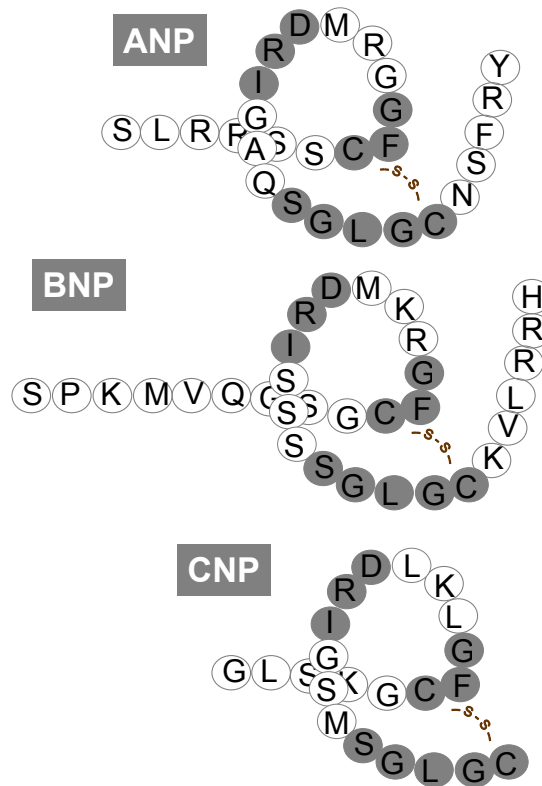


Figure 1. Structure of human atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). All three peptides have the ring structure formed by a disulfide bridge between two cysteine residues and share 11 amino acids which are presented as gray circles.

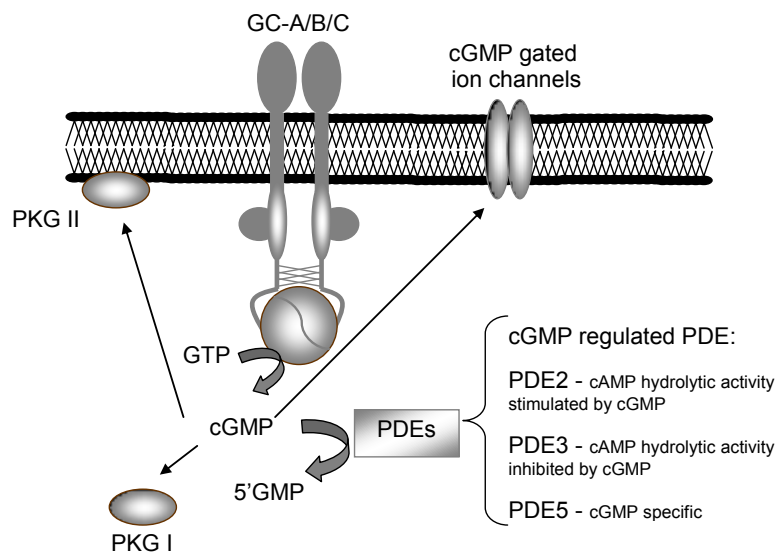


Figure 2. Signaling pathway of natriuretic peptides. Activation of guanylate cyclase A, B and C (GC-A/B/C) also known as natriuretic peptide receptor A and B (NPR-A/B) and GC-C for guanylin peptides leads to intracellular increase in cGMP concentration. cGMP activates soluble protein kinase G I (PKG I) or membrane bound protein kinase G II (PKG II) as well as ion channels and cGMP dependent phosphodiesterases (PDE).

the brain. However, the physiological effects of intestinal natriuretic peptides in the brain are still unknown [46]. GC-A, GC-B and GC-C are consistent of distinctive parts. These are the extracellular domain, transmembrane region, kinase-like domain and guanylate cyclase catalytic domain (Figure 3) [47,48]. The NPR-C does not have guanylate cyclase activity and it mainly functions as a clearance receptor (Figure 3). It binds ANP, BNP, and CNP which results in endocytosis, hormonal degradation, activation of pertussis toxin sensitive G-protein and inhibition of adenylate cyclase (responsible for increasing intracellular cAMP concentration) and protein kinase C [49-52]. mRNA for NPR-C is located in the kidney, heart, cerebral cortex and cerebellar tissue (see Table 1) [53]. It was suggested that the mechanism by which NPs display a neuromodulatory effect involved inhibition of PKC by NPR-C [54]. In cultured rat astrocytes, activation of NPR-C led to the inhibition of DNA synthesis and consequently the suppression of cell proliferation [55].

Other isoforms of guanylate cyclases (GC-D, GC-E, GC-F) are located in sensory organs but their ligands are still unknown [56-60]. Recently it was shown that GC-D is activated by bicarbonate ions [61]. Another guanylate cyclase named G (GC-G or GC-1) is an orphan receptor located in skeletal muscles, lung and intestine. Current research has shown that GC-G is the only type of guanylate cyclase present in principal cells of the cortical collecting duct in the rat kidney [62-64].

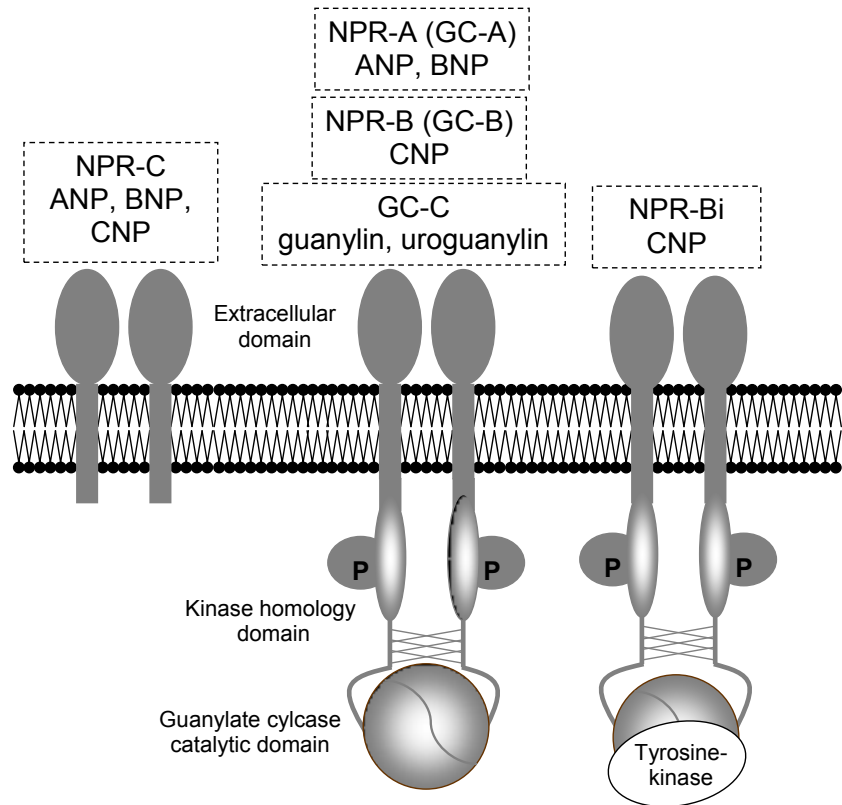
## 2. Natriuretic peptides and neuronal function

cGMP, regardless of its source (NO, and soluble guanylate cyclase or NPs and their

receptors) plays an important role in brain physiology. Its actions are of particular importance regarding modulations of long-term changes of synaptic activity in the hippocampus, amygdala, cerebellum (by pre-synaptic transmitter release [65]) and post-synaptic functions via activation of different PKG isoforms [66,67]. ANP negatively

modulates noradrenergic neurotransmission by inhibiting  $K^+$ -induced  $Ca^{2+}$  uptake which decreases the norepinephrine release at the pre-synaptic site of the neurons [68].

Furthermore, cGMP signaling pathways (both NO and NPs related) change during neuronal development. ANP binding receptor(s) are up-regulated during neuronal differentiation (in the



**Figure 3.** Structural differences between natriuretic peptide receptor A and B (NPR-A/B) and clearance receptor known as natriuretic peptide receptor C (NPR-C) which shows no guanylate cyclase activity. The NPR-Bi receptor is a splice variant of the NPR-B receptor which also has no guanylate cyclase activity but it most likely displays tyrosine kinase-like activity. NPR-A is the receptor for atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) while NPR-B is specific for the C-type natriuretic peptide (CNP). The clearance receptor NPR-C binds all three natriuretic peptides.

**Table 1.** Expression of natriuretic peptides and their receptors in mammalian central nervous (modified from Cao LH *et al* 2008 [73]).

|                   | ANP             | BNP    | CNP    | NPR-A    | NPR-B    | NPR-C    |
|-------------------|-----------------|--------|--------|----------|----------|----------|
| Cerebral cortex   | weak            | strong | strong | moderate | moderate | strong   |
| Amygdaloid nuclei | moderate        | weak   | strong | weak     | moderate | strong   |
| Hypothalamus      | strong          | strong | strong | strong   | strong   | strong   |
| Cerebellum        | scattered cells | weak   | strong | weak     | moderate | moderate |
| Hippocampus       | scattered cells | weak   | weak   | weak     | weak     | moderate |
| Retina            | weak            | weak   | weak   | weak     | weak     | moderate |

telencephalon in E13 mice, dorsal root ganglion cells and peripheral nerves in E14 mice). The highest ANP binding was seen in the rat cortical neuroepithelial cells at E17. ANP binding sites mostly correspond to localization of clearance receptor NPR-C but not GC-A receptor [69-71]. Thus, it is not surprising that an increase of intracellular cGMP concentration by activation of GC-A is not substantial in differentiated cells [72].

Recent studies showed a neuroprotective role of NPs and the cGMP signaling pathway. An increase of intracellular cGMP concentration protects neurons against excitotoxic, metabolic, oxidative damages as well as *N*-methyl *D*-aspartate (NMDA)-induced neurotoxicity [73].

### 3. Natriuretic peptides and glial cells

Glial cells with the necessary expressed proteins for NP signaling are proposed to be a

source and target of NPs where they could be involved in glia communication with neurons and brain capillaries [31,74]. However, some of the published effects of cGMP on glial cells are not proven to be due to action of NPs but are more likely due to the presence of the NO system and activation of soluble guanylate cyclase.

During ischemic stroke and brain injury astrocytes can swell due to changes in pH and increase in extracellular K<sup>+</sup> concentration. Since NPs regulate ion and water transport as well as pH-regulating transport systems in kidney cells, it is not surprising that NPs inhibit osmotic swelling in astrocytes [75]. CNP influences ion transport by inhibiting Na<sup>+</sup>/H<sup>+</sup> exchanger and thereby lowers the intracellular pH [76]. It also increases expression of the most important aquaporin (type 4) present in astrocytes responsible for brain water transport via the blood-brain barrier and cerebrospinal fluid [77].

### 4. Conclusion

Despite the abundance of the evidence suggesting that NPs play an important physiological role in certain pathophysiological conditions such as stroke and brain trauma, there still remain many unanswered questions. Future investigations need to address the variety of NPs, their receptors and the signaling pathways involved in the brain. To be able to use potential beneficial effects of NPs studies should identify the effects of NPs on the immunological response, neurons and glial cells during pathological conditions.

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