



Review

Natriuretic peptides and cerebral hemodynamics

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ABSTRACT

Natriuretic peptides have emerged as important diagnostic and prognostic tools for cardiovascular disease. Plasma measurement of the bioactive peptides as well as precursor-derived fragments is a sensitive tool in assessing heart failure. In heart failure, the peptides are used as treatment in decompensated disease. In contrast, their biological effects on the cerebral hemodynamics are poorly understood. In this mini-review, we summarize the hemodynamic effects of the natriuretic peptides with a focus on the cerebral hemodynamics. In addition, we will discuss its potential implications in diseases where alteration of the cerebral hemodynamics plays a role such as migraine and acute brain injury including stroke. We conclude that a possible role of the peptides is feasible as evaluated from animal and in vitro studies, but more research is needed in humans to determine the precise response on cerebral vessels.

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1. Introduction

Natriuretic peptides comprise a family of structurally related hormones consisting of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) [1]. The primary effect of the hormones is to maintain cardiovascular homeostasis

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by affecting central and peripheral hemodynamics [2,3]. Since their discovery in the 1980s, the diagnostic importance of natriuretic peptide measurements has increased tremendously, especially in the field of clinical cardiology [4–6].

ANP and BNP are systemic hormones predominantly produced in the heart [7,8], but also expressed in the central nervous system and the vascular system [9–12]. CNP acts predominantly in a paracrine manner [13,14] and is produced in the brain and blood vessels [15,16].

All of the natriuretic peptides have vasodilatory [17–21], diuretic and natriuretic [22] effects that influence the intravascular volume [23,24]. In contrast, the selective effects on the cerebral circulation are poorly understood. The responsiveness of cerebral vessels and cerebral vascular smooth muscle cells to natriuretic peptides has yet to be determined in humans. The purpose of this mini-review is, therefore, to summarize the physiological effects of the natriuretic peptides with a particular focus on the cerebral hemodynamics. In addition, we will discuss its potential implications in diseases where alterations of the cerebral hemodynamics play a role e.g. migraine and acute brain injury including stroke.

1.1. Methods

All articles in this review were found using PubMed based on the following search terms: natriuretic peptide, atrial, brain, C-type, ANP, BNP, CNP, atrial natriuretic factor, ANF, atriopeptin, vascular, vasodilatation, in vivo, in vitro, cerebral, circulation, hemodynamic, migraine, stroke, traumatic brain injury, acute brain injury, subarachnoid hemorrhage, heart, artery, veins, temporal artery, external carotids, extracranial vessels, cerebral blood flow, inflammation, renal, radial, heart failure, endothelial and atherosclerosis.

2. Distribution of the natriuretic peptides

Natriuretic peptides are widely distributed in numerous tissues of the body [9,11,25]. ANP is, however, mainly produced in the atrial cardiomyocytes [7]. Release of ANP is of a pulsatile pattern [26] and is rapidly stimulated by tension of the atria caused by increased venous return. ANP release can also be stimulated by prostaglandins, angiotensin II, endothelin-1 and myocardial hypoxia [27–31].

BNP is produced both in atrial and ventricular cardiomyocytes and often referred to as a “second line” hormone [32]. It is released in response to increased wall tension of the cardiac ventricles [33–37] but may also be influenced by postural changes, low oxygen supply, angiotensin II and endothelin-1 [33–37].

CNP is mainly produced in the brain and in the vascular endothelium [15,16]. Production and release of CNP is stimulated by transforming growth factor (TGF) and by the levels of foremost BNP but also by ANP [38]. The physiological effects of CNP are predominantly local/paracrine and the concentration in circulation is low [39,40].

Although the natriuretic peptides pass the blood–brain barrier (BBB) poorly [41], they are all expressed in the central nervous system [25,42]. ANP is mostly expressed in the hypothalamus [43]. BNP and CNP are widely distributed in the central nervous system including the cerebral cortex, thalamus, hypothalamus, pons and spinal cord. BNP, however, is undetectable in the cerebellum, whereas CNP is absent in the striatum [25,42]. Neurohormones such as endothelin, vasopressin and norepinephrine have been shown to stimulate the release of ANP from cultured hypothalamic neurons [44–46]. The natriuretic peptides also act in the brain stem to decrease sympathetic tone [47,48]. The actions of the natriuretic peptides in the brain enhance those in the periphery and imply a coordinated central and peripheral action in controlling fluid and electrolyte homeostasis. Furthermore, ANP has also been shown to possess anxiolytic activity by an unknown mechanism [49].

Two major routes of degradation exist for the natriuretic peptides; via a clearance receptor and via the enzyme neutral endopeptidase (NEP). The affinity of these paths to each peptide highly influences the

half-lives of each peptide, possibly explaining why BNP has the longest half-life compared to ANP and CNP.

3. Receptors and mechanisms of action

3.1. Receptors

Three natriuretic peptide receptors (NPRs) have been identified, namely NPR-A, NPR-B and NPR-C [50].

NPR-A is a transmembrane receptor that binds ANP and BNP with the greatest affinity for ANP [51]. It is primarily expressed on outer membranes of endothelial cells and vascular smooth muscle cells of both the arterial and venous systems [38]. The receptor is also expressed on neurons [52] and other tissues [53–55]. Several studies have suggested that NPR-A is downregulated during chronic stimulation due to increased concentrations of ANP and BNP [56–58], leading to a relative hyporesponsiveness to these peptides [18].

NPR-B is also a transmembrane receptor that preferably binds CNP [51] and is localized in the brain and the vascular system, especially veins [59,60].

NPR-C is mostly a clearance receptor [51] that binds all natriuretic peptides with equal affinity and constitutes 95% of the existing NPR [61]. When the natriuretic peptides bind to NPR-C, they undergo receptor-mediated endocytosis and lysosomal degradation. Besides being a clearance receptor, however, NPR-C can also mediate other biological actions [62,63]. It is primarily found on veins, the kidneys and the lungs [20,64].

The NPRs are highly expressed in neuronal structures, but their neuro-modulatory functions remain largely unknown. In animals, NPR-A, NPR-B and NPR-C are present in brainstem structures including the periaqueductal gray (PAG), locus coeruleus (LC) and trigeminal motor nucleus [65–67]. NPR-A and NPR-B are also present in the dorsal root ganglions (DRGs) and the spinal cord [52,68].

3.2. Mechanisms of action

The vasoactive effects are mediated by several mechanisms, but the key one is activation of the cyclic guanosine monophosphate (cGMP) pathway. Natriuretic peptides activate the membrane bound particulate guanylate cyclase (pGC) by binding to NPR-A or NPR-B [2,9,50]. pGC catalyzes the transformation of guanosine triphosphate (GTP) to cGMP [69,70]. In turn, increased intracellular cGMP levels result in lower calcium (Ca^{2+}) concentrations [71], which induces vasodilation [63]. cGMP also modulates the activity of Ca^{2+} -activated potassium (K^+) channels and adenosine triphosphate (ATP)-sensitive K^+ channels which also affect vessel diameter [72].

Vasodilatation can also be mediated by NPR-C upon CNP binding which provokes hyperpolarization of smooth muscle cells in the vascular system [62]. Furthermore, several studies suggest that natriuretic peptides are able to stimulate nitric oxide (NO) production [63,73–75], which is probably mediated by the NPR-C affecting nitric oxide synthase (NOS) production [63]. In contrast to the activation of the transmembrane pGC through NPR-A and -B, NO exerts vasodilation through an intracellular cytosolic enzyme, soluble guanylate cyclase (sGC) [76]. Both of these GC-systems result in an increase of intracellular cGMP levels [70]. Moreover, an autoregulatory link between the paracrine activity of NO and CNP and the endocrine functions of ANP and BNP exists. When either the sGC or the pGC system increases in sensitivity, the other system also increases in sensitivity even at low levels [70].

In summary, the NPRs are highly expressed in the vascular and neuronal systems. They mediate direct vasoactive effects via activation of pGC but also indirect effects by inducing NO production. The function of the NPRs in the nervous system is a rather unexplored area yet to be described.

4. Hemodynamic effects

ANP and BNP have similar effects and both have significant hemodynamic properties, which include an increase of heart rate (HR) and fall in mean arterial blood pressure (MAP), as well as being natriuretic and diuretic [77–80]. CNP, however, does not affect blood pressure, heart rate or diuresis [13,14] except in extremely high doses (430 pmol/kg bolus) [81].

The hemodynamic effects are caused by a combination of different mechanisms: 1) reduction in cardiac preload, possibly by lowering venous return due to increased venous capacitance [80,82]. 2) Shifting of intravascular fluid into the extravascular compartment [83] which reflects increased permeability of the vascular endothelium. 3) Natriuresis and diuresis by affection of the kidneys [84,85]. 4) Neurohumoral effects by suppressing the renin–angiotensin–aldosterone system (RAAS) and aldosterone [40]. Furthermore, ANP can also modulate the autonomic nervous system by sensitizing arterial and cardiac baroreceptor afferent nerve endings, thus inhibiting sympathetic ganglionic neurotransmission by a central neural action [47,86–89]. This suppresses the reflex tachycardia and vasoconstriction that accompany the reduction in preload, ensuring a sustained decrease in blood pressure.

Infusion of low dose ANP (0.05 µg/kg/min) in healthy subjects has not shown clear effects on MAP and HR, but a high dose infusion (>0.1 µg/kg/min) leads to a significant change in blood pressure and HR [78,90,91]. ANP infusion in heart failure patients shows mostly no effect on HR and MAP, but a fall in vascular resistance has been noted [92].

Low dose (0.003–0.01 µg/kg/min) BNP infusions in healthy subjects display little effects on MAP and HR [80,93–95], but high dose infusions of BNP (0.1 µg/kg/min) lead to a marked increase in HR, a reduction in MAP, a fall of peripheral vascular resistance and increased diuresis [96,97]. In heart failure patients both low and high dose BNP had a significant effect on hemodynamics [96,98,99].

Low and high dose infusion of CNP in humans do not induce any significant changes in HR and MAP [13,14,100,101]. Presence of cardiovascular CNP effects on the hemodynamic side in humans is still controversial as is its endocrine role.

5. Vasoactive effects

In humans, the natriuretic peptides all have different preferences in what part of the vascular system to act upon. At first, it was believed that the peptides primarily act on arteries but it appears that the venous system also plays an important role [102].

Infusions of all three peptides into brachial arteries of healthy men induce a dose-dependent increase of forearm blood flow by dilating forearm resistance vessels [18,57,74,17,103,104]. ANP is more potent than BNP with CNP being the least potent [17].

The effects of natriuretic peptides on the microcirculation are less examined. Infusion of low dose BNP in healthy subjects does not induce changes in the microcirculation of the skin or the conjunctiva [94]. In contrast, low dose infusion of ANP in healthy subjects results in vasoconstriction of the microcirculation [19]. The vasoconstrictive properties of the natriuretic peptides have also been observed in other studies and are mostly seen in the kidneys [39,105], but the mechanisms behind are yet unknown.

In vitro studies on human radial and internal mammary arteries have shown that ANP, BNP and CNP all possess dose-dependent dilatory effects [20,21]. In the saphenous veins, all peptides also had dilatory effects albeit less in magnitude [20,21]. However, the effects of ANP and BNP on human resistance arteries vary depending on the anatomical site of the artery [104,106]

Furthermore, it has been shown that a low dose of BNP primarily induces venous dilation, whereas arterial dilation occurs at higher BNP doses only [20].

In summary, it appears that ANP may preferentially act on arteries and thus afterload, whereas BNP preferentially acts on veins and thus

preload. ANP seems to be the most potent peptide while CNP seems to be the least potent [20]. However, the exact effects of natriuretic peptides on microcirculation and resistance arteries are yet unclear [20,21].

6. Cerebral circulation

The effects of natriuretic peptides on the cerebral circulation are very sparsely studied. As far as we know, no studies of the vasoactive effects on the cerebral vessels and cerebral blood flow (CBF) have been performed in humans. Furthermore, no articles describing the effect of natriuretic peptides on extracranial vessels such as the temporal or external carotid arteries could be found. Only in vitro animal studies and a single in vivo study on cerebral vessels have been published (Table 1).

6.1. Cephalic vessels

ANP is a potent dilator of precontracted guinea pig basilar arteries in vitro [107].

In rats, application of ANP and BNP to the extraluminal side of the middle cerebral artery (MCA) had little or no dilatory effect whereas CNP dilated the vessels significantly [108]. In pigs, CNP but not ANP dose-dependently increased cGMP in cerebral arterial smooth muscle cells from the basilar artery, anterior and middle cerebral arteries and internal carotid artery [109]. In rats, pre-constricted cerebral arteries did not undergo relaxation in response to ANP [110]. In contrast, a feline in vivo study suggested that the diameter of the pial artery increases after subarachnoid perivascular microapplication of ANP in an open skull preparation [111].

In vitro studies of rat cerebral micro-vessels from the cortex have shown inconsistent results by measuring increase in cGMP levels. One study showed a dose-dependent response to both ANP and CNP, with ANP being the most potent peptide [112], whereas another study showed that CNP was most potent compared to ANP and BNP [113].

ANP dilates pial arterioles from rabbits when applied topically but not when administered intravenously [114]. ANP also produces a decrease in the resistance in large arteries of the cerebral circulation when infused in rabbit carotid arteries [115].

No articles on natriuretic peptide effects on meningeal and extracranial vessels such as the temporal artery or external carotids could be retrieved in either human or animals.

6.2. Cerebral blood flow

Cerebral blood flow (CBF) is determined by a number of factors, such as dilation of cerebral blood vessels and cerebral perfusion pressure, which is determined by the systemic blood pressure. Natriuretic peptides may cause changes in the CBF not only due to their ability to regulate the systemic circulation but also due to their ability to change vessel diameter and possible vasodilation locally in the brain [116].

Intracortical injection of ANP in rats produces a decline in regional CBF [117], indicating possible vasoconstriction, whereas a study in rabbits showed no increase in CBF after intracarotid administration of large doses of ANP [115].

An increase in CNP release from cerebral locations during hypercapnia has been reported, indicating a possible role of CNP in CO₂ modulated CBF responses [118].

The results are contradictory and inconsistent with regard to what response natriuretic peptides elicit in the cerebral circulation. The experiments were performed in different animals albeit with similar doses of the natriuretic peptides. The difference could perhaps also be due to the study of different vessels [109,112]. Overall, the effects of natriuretic peptides on the cerebral vessels are yet controversial, and further studies are required to fully elucidate their effects on cerebral hemodynamics, especially in humans.

Table 1
Effects of natriuretic peptides on cerebral vessels in experimental animal studies.

Study	NP	Animal	Vessel	Vasoaction	cGMP	Year
<i>ANP</i>						
Macrae et al. [111]	ANP	Cats ^a	Pial arterioles of cortex	↑	X	1987
Kruuse et al. [107]	ANP	Guinea pig	Basilar artery	↑	X	2001
Iida et al. [114]	ANP	Rabbit	Pial arterioles (topically)	↑	X	2001
			(intravenously)	=	X	
Tamaki et al. [115]	ANP	Rabbit	Large cerebral arteries	↑	X	1992
Osol et al. [110]	ANP	Rat	Posterior cerebral artery	=	X	1986
Kobayashi et al. [112]	ANP	Rat	Cerebral microvessels (cortex)	X	↑	1994
Mori et al. [108]	ANP	Rat	Cerebral arterioles and MCA	=	X	1997
Vigne et al. [113]	ANP	Rat	Cerebral microvessels from cortex	X	(↑)	1992
Tao et al. [109]	ANP	Pig	Cerebral arterial smooth muscle cells	X	=	1995
<i>BNP</i>						
Mori et al. [108]	BNP	Rat	Cerebral arterioles	=	X	1997
Vigne et al. [113]	BNP	Rat	Cerebral microvessels (cortex)	X	(↑)	1992
<i>CNP</i>						
Mori et al. [108]	CNP	Rat	Cerebral arterioles	↑	X	1997
Tao et al. [109]	CNP	Pig	Cerebral arterial smooth muscle cells	X	↑	1995
Vigne et al. [113]	CNP	Rat	Cerebral microvessels (cortex)	X	↑	1992
Kobayashi et al. [112]	CNP	Rat	Cerebral microvessels (cortex)	X	↑	1994

NP: natriuretic peptide; MCA: middle cerebral artery; X: no information in the article, =: unchanged, ↑: dilatation, (↑): small dilatation, ↓: constriction.

^a In vivo, all other studies were performed in vitro.

7. Clinical relevance

In the last decade, natriuretic peptides have emerged as important diagnostic and prognostic tools for cardiovascular diseases due to their elevated plasma concentrations in these conditions [6,9,119]. Furthermore, synthetic ANP (Carperitide) and BNP (Nesiritide) are used by cardiologists in the US and Japan, respectively, as a therapy for heart failure patients due to their vasodilatory and diuretic activities [90,120], and they have shown to improve the hemodynamic function and clinical status of these patients. However, natriuretic peptide related mechanisms may also contribute to the understanding of the pathophysiology of neurovascular diseases such as migraine and stroke.

7.1. Migraine

The ability of natriuretic peptides to activate the cGMP-dependent pathway via pGC and NO in vascular cells as well as identification of the peptides and their receptors in migraine-relevant pathways indicate that they may have a role in the pathophysiology of migraine.

Migraine is a highly prevalent and costly neurological disorder [121]. Its initiating mechanisms are complex but can involve the cGMP signaling pathway based on studies with sildenafil and glyceryl-trinitrate (GTN) [122,123]. Administration of sildenafil and GTN induces migraine-like attacks in about 80–85% of migraine patients without aura, most likely by increasing intracellular cGMP concentration of endothelial and vascular smooth muscle cells in cerebral arteries [122, 123]. GTN releases NO which activates the sGC, while sildenafil causes intracellular cGMP accumulation by inhibiting phosphodiesterase-5 (PDE5) [123]. It would, therefore, be of interest to examine whether the natriuretic peptides can induce migraine attacks in migraine patients.

Moreover, all known pharmacological triggers of migraine possess vasoactive properties and are potent vasodilators like the natriuretic peptides [122–124]. However, a simple dilatation of cerebral arteries cannot alone explain migraine pain during migraine attacks [125]. Migraine pain is likely due to sensory input from perivascular trigeminal nociceptors and subsequent activation of brain stem structures such as PAG, nucleus raphe magnus (NRM) and LC [126,127]. Natriuretic peptides and their NPRs are present in this migraine relevant pain pathway. ANP, BNP and their cognate receptor (NPR-A) are expressed in the trigeminal ganglion [128,129], trigeminal spinal nucleus [130], PAG,

NRM and LC [43,65,129]. NPR-B and NPR-C are also present in the trigeminal spinal nucleus, PAG, NRM and LC [66,67] (Table 2 and Fig. 1).

Furthermore, BNP [68], NPR-A and NPR-B are co-localized with calcitonin-gene-related peptide (CGRP) in the DRG [52,68]. CGRP plays a key role in migraine pathophysiology [131]. It has been shown that intravenous infusion of CGRP triggers migraine attacks [124] and antagonists to CGRP receptor are effective for the acute treatment of migraine [132,133]. Whether natriuretic peptides exert a similar action in migraine is yet to be examined.

The ability to enhance vascular permeability [24,83] is interesting in the aspect of migraine and natriuretic peptides. ANP affects the amount of intravascular fluid by altering the permeability for albumin in endothelial cells [23] and has the ability to hinder changes in vascular permeability induced by other molecules [134]. It would be plausible to suggest that this change in permeability may initiate perivascular inflammation and activate nerve endings. Neurogenic inflammation is an important component in migraine pathophysiology [135,136] and the resulting sensitization of perivascular sensory nerves might be the activator of migraine pain [126] (Fig. 1).

Substances known to induce migraine attacks in migraine patients are able to induce headache in healthy volunteers [137]. The possible headache inducing properties by the natriuretic peptides via pGC are unclear, but interestingly headache was reported as an adverse event in trials with Nesiritide [120,138]. Furthermore, it has been reported that migraine patients have higher levels of pro-inflammatory cytokines and pro-BNP and lower levels of anti-inflammatory cytokines compared to controls [139].

In summary, natriuretic peptides seem to share many properties with known migraine-inducing substances, thereby indicating a role

Table 2
Distribution of natriuretic peptides and its receptors in migraine-relevant structures.

	TG	SPY	STN	PAG	NRM	LC
ANP	X [128]			X [43]		X [43]
BNP	X [129,161]	X [161]			X [129]	X [129]
CNP						
NPR-A	X [130]		X [65]			X [65]
NPR-B			X [66]	X [66]	X [66]	X [66]
NPR-C				X [67]		X [67]
mRNA CNP			X [162]			

TG: trigeminal ganglion, SPY: sphenopalatine ganglion, STN: spinal trigeminal nucleus, PAG: periaqueductal gray, NRM: nucleus raphe magnus, LC: locus coeruleus.

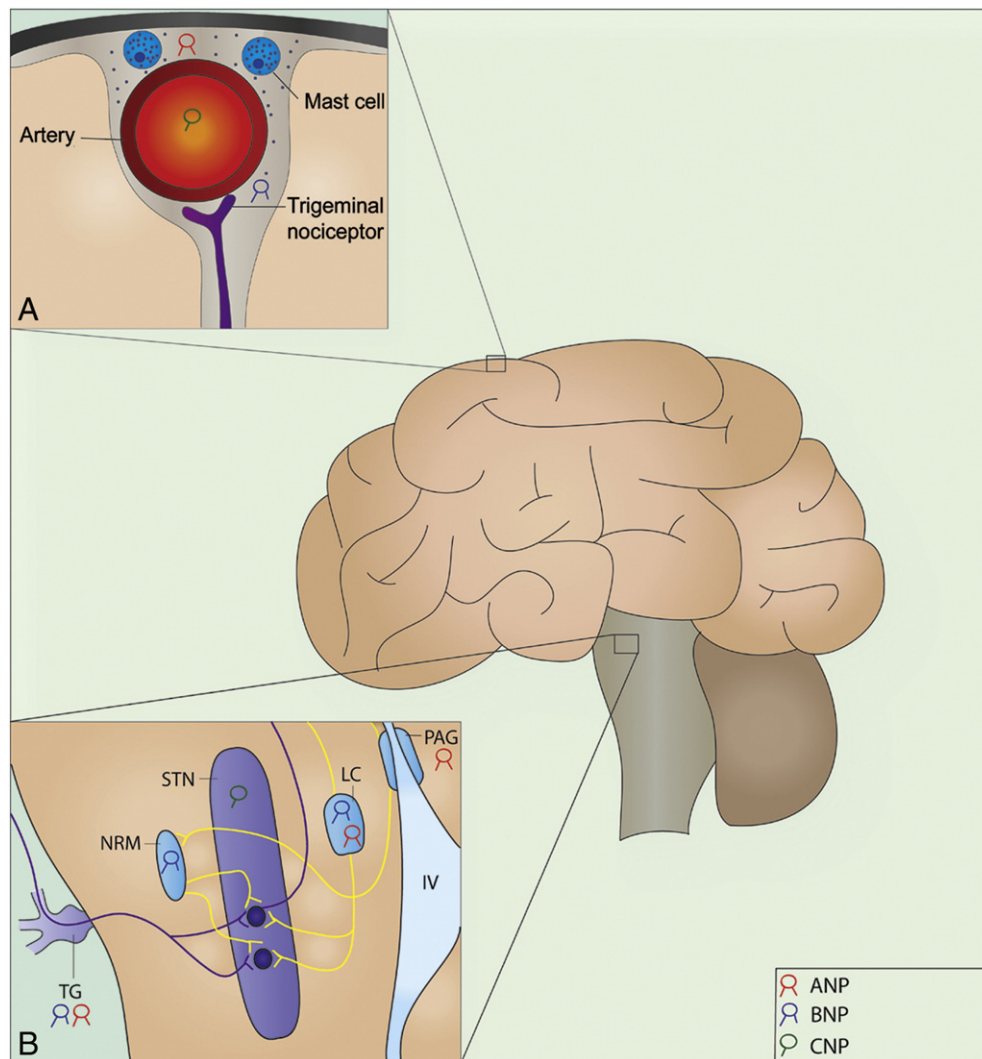


Fig. 1. The proposed involvement of natriuretic peptides in the pathogenesis of migraine. Inset A: The vasoactive effects of the natriuretic peptides including vasodilation and induced vascular permeability may lead to perivascular inflammation and neurogenic inflammation through mast cell degranulation and sensitization of perivascular nerve endings. Inset B: Natriuretic peptides and their receptors have been identified in the trigeminovascular system and other migraine relevant structures and may here act through, yet unidentified, mechanisms to promote pain. ANP: atrial natriuretic peptide, BNP: brain natriuretic peptide, CNP: C-type natriuretic peptide, TG: trigeminal ganglion, STN: spinal trigeminal nucleus, PAG: periaqueductal gray, NRM: nucleus raphe magnus, LC: locus coeruleus, IV: fourth ventricle.

of natriuretic peptides in migraine. Studies with natriuretic peptides in both healthy volunteers and migraine patients may contribute to a better understanding of the intracellular mechanisms during migraine attacks. If the natriuretic peptides are implicated in migraine, NEP or NPR-C may represent a new target for the development of migraine treatments.

7.2. Acute brain injury

Several studies have demonstrated that serum BNP levels increase after stroke [140–142], subarachnoid hemorrhage (SAH) [143–145] and traumatic brain injury (TBI) [146–148]. However, the pathophysiological mechanism underlying this association is unknown. In particular, it is unclear whether BNP has a neuroprotective or neurotoxic role after acute brain injury.

James et al. [149] reported that BNP improved neurological function in a rat model of acute brain injury and was associated with enhanced CBF and downregulation of neuroinflammatory responses. ANP has been shown to have an effect on ischemic brain edema, possibly by suppressing the elevation of water content through regulation of electrolyte transport in the brain [150]. The natriuretic peptides might also have a

potential role in the pathophysiology of SAH and cerebral vasospasm (CVS). It has been proposed that natriuretic peptides activate NO–cGMP signaling in CVS [153]. This role, however, is probably paradoxical due to the contradiction of their local and systemic effects [116] (Fig. 2).

By their local effects, the natriuretic peptides may act as a protective hormone due to its potent vasodilator and anti-angioproliferative properties [20,151]. ANP and BNP also have potent inhibitory effects on endothelin secretion [152–154]. These antagonistic activities can lead to a reduction in the intensity of the CVS [155] and improvement in the CBF. Josko et al. [156] proposed that increased natriuretic peptide secretion is a counter-mechanism in which the brain is protected against ischemic insult caused by vasospasm. This particular study showed that chronic CVS following SAH enhances the ANP secretion. These compensatory and regulatory mechanisms may help prevent the development of brain edema and the progression of vasospasm [156].

Natriuretic peptides may also potentiate CVS through their systemic effects including reduction of blood pressure and blood volume [40] and can therefore decrease CBF and augment cerebral ischemia secondary to vasospasm [116].

BNP plasma concentrations are elevated during the acute phase in patients with stroke, SAH and TBI, and correlate with poor outcomes

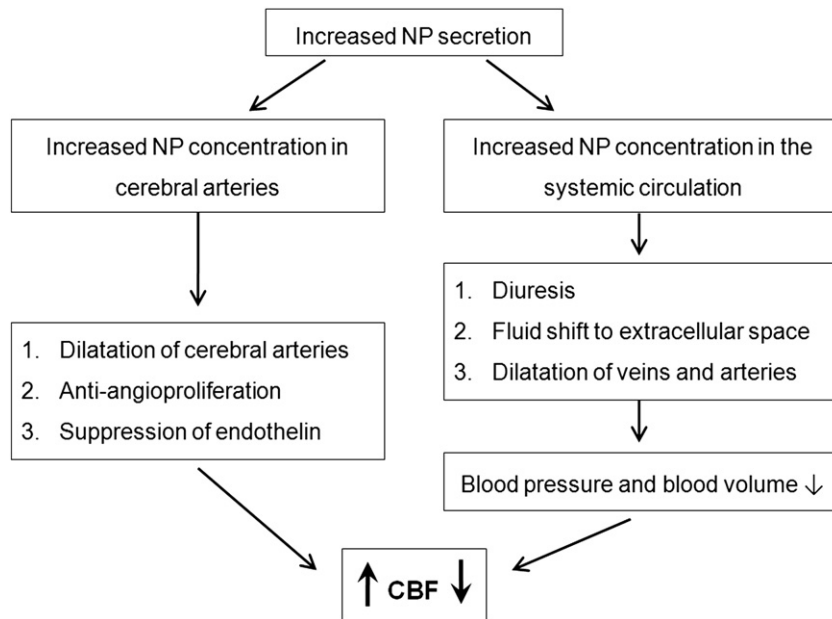


Fig. 2. Proposed hypothesis for local and systemic effects of natriuretic peptides on cerebral blood flow (CBF) and cerebral vasospasm.

and mortality [147,157]. Two studies suggested that the increase of BNP levels could be the cause of cerebral salt wasting syndrome, which is characterized by hyponatremia and natriuresis after SAH [144,145]. High BNP levels after TBI could lead to elevation of intracranial pressure (ICP) and malignant brain edema [147,148]. There are, however, also studies showing no association between BNP, sodium levels or outcome [158–160].

Based on existing data, it is uncertain whether natriuretic peptides: 1) play an adaptive role in recovery after acute brain injury through augmentation of CBF or 2) decrease CBF by its systemic effects or 3) induce steal phenomena by shunting perfusion to normal areas of the brain due to increase of regional CBF. The role of natriuretic peptides after acute brain injury therefore remains controversial. To our knowledge, no in vivo studies on the vasoactive properties of the natriuretic peptides on cerebral arteries or CBF have been conducted in humans. Therefore, future studies focussing on the properties of the natriuretic peptides on the cerebral circulation are warranted.

8. Conclusion

Remarkably little is known about the role of natriuretic peptides in cerebral hemodynamics in humans. Therefore, we believe that it will be important to obtain an extensive and precise description of the peptide effects on cerebral hemodynamics, as many factors remain unknown. It would be interesting to investigate the migraine inducing properties of the natriuretic peptides and its vasodilatory effects on the cerebral vessels. In perspective, this could lead to new insight into neurovascular diseases and perhaps pave the way for novel therapeutic targets.

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Conflict of interest

There are no conflicts of interest in relation to this paper.

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