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Role of cardiac biomarkers in cognitive impairment and functional decline

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CHAPTER 6

NATRIURETIC PEPTIDES IN THE BRAIN: NOVEL TARGETS FOR COGNITIVE IMPAIRMENT

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Abstract

Natriuretic peptides (NPs) are traditionally known as cardiac hormones with diuretic, natriuretic and blood pressure lowering properties. Evidence indicates that NPs and their receptors are abundant in the central nervous system, suggesting their involvement in regulation of various brain functions. It has been shown that NPs are involved in the regulation of neurovascular and blood-brain barrier integrity, neuro-inflammation, neuroprotection, synaptic transmission and brain fluid homeostasis. In addition, NPs might contribute to the brain's inhibitory control over the hypothalamic-pituitary-adrenal axis. Studies have also shown that high systemic levels of NPs are associated with cognitive impairment independent of cardiovascular risk factors. In this review we discuss the potential roles of NPs in regulating structural and functional integrity of the brain. Based on the available neurobiological and clinical evidence, we propose that NPs might represent as potential novel diagnostic and therapeutic targets for cognitive impairment.

Introduction

Natriuretic peptides (NPs) are commonly recognized as cardiac hormones regulating several cardiovascular functions. This family comprises three members, namely atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). These peptides are involved in the control of body fluid homeostasis and have natriuretic, diuretic and vasodilatory properties¹.

Increasing evidence shows that elevated plasma levels of NPs are associated with accelerated cognitive decline. While higher circulating levels of NPs are correlated with cardiovascular risk factors and impaired cardiac function², we and others have shown that the association between circulating NPs and cognitive impairment is independent of cardiac and cardiovascular factors³⁻⁵. This independent association might suggest that NPs directly influence the brain and its vasculature. Indeed, all three NPs and their receptors are abundantly present in the central nervous system (CNS) and regulate various CNS functions. It has been shown that NPs are involved in the regulation of neurovascular and blood-brain barrier integrity, neuro-inflammation, neuroprotection, synaptic transmission, the stress responsive hypothalamus-pituitary-adrenal (HPA) axis, and brain fluid homeostasis⁶. Since disturbances in these functions have been implicated as potential mechanisms for cognitive impairment and dementia, any disruptions in the activity of NPs in the CNS might affect the integrity of the brain and lead to cognitive impairment.

In this review, we provide a brief overview of the roles of NPs in various aspects of CNS physiology and discuss their relevance to cognitive impairment and dementia in the context of amyloid beta (A β) and tau protein depositions, neurovascular dysfunction, neuro-inflammation, neuronal damage, synaptic failure, anxiety and disturbed fluid homeostasis in the CNS. Given the available neurobiological and clinical evidence, we propose that NPs might serve as potential novel diagnostic and therapeutic targets for cognitive impairment.

Molecular structure and localization of NPs and their receptors in the CNS

All NPs share a ring structure of 17-amino-acides mediated by a disulfide bridge between two cysteine residues⁷. The amino acid sequence of human ANP and BNP consist of 28 and 32 amino-acids, respectively. In the human CNS, the molecular weight of BNP was suggested to be larger than that of BNP-32 and the molecular structure of ANP was found to be different than that of ANP in the heart⁸. It was shown that immunoreactive CNP contains 22 or 53 amino-acids, with the CNP-53 being the predominant form in human brain⁹.

NPs bind to specific types of membrane receptors to exert their biological functions. Three receptors for NPs include natriuretic peptide receptor A (NPR-A), natriuretic peptide receptor B (NPR-B) and natriuretic peptide receptor C (NPR-C). It has been shown that all three NPs have similar affinity for NPR-C, while ANP and BNP bind primarily to NPR-A and CNP binds to NPR-B with high specificity¹⁰. NPR-A and NPR-B share four structural features: an extracellular domain, a transmembrane region, a kinase-like domain and a guanylate cyclase catalytic domain. Activation of these receptors increases the intracellular concentration of cyclic guanosine monophosphate (cGMP), which has been shown to regulate most of the biological effects of NPs¹¹. NPR-C lacks the guanylate cyclase catalytic domain and functions mostly as a clearance receptor¹², although there is evidence for a signaling function of this receptor as well¹³.

Shortly after discovery of NPs in the rat myocardia¹⁴, all NPs have been found to have extensive distribution in rodent and human CNS. The distributions of CNP and BNP in the CNS were shown to be higher than that of ANP. It was shown that in human brain the level of CNP-like immunoreactivity is 10 times higher than that of ANP or BNP, suggesting that it mainly functions in the CNS¹⁵. Evidence from animal studies showed highest concentration of NPs in the hypothalamus, and abundant concentrations in the telencephalon, cerebellar cortex, spinal cord and retina¹⁶. Human studies showed the presence of CNP and BNP in the cerebral cortex, thalamus, hypothalamus, pons and cerebellum, with CNP having the highest concentrations in the hypothalamus^{8, 17}. In human

brain autopsy samples, the highest concentration of ANP was found in the preoptic, supraoptic and paraventricular nuclei of the hypothalamus, choroid plexus and ventricular ependymal cells¹⁸. ANP was also detected in the brain stem, cerebral cortex, basal nuclei and thalamus of human CNS¹⁸. Furthermore, all NPs have been detected in human cerebrospinal fluid (CSF) with CNP being the most abundant type¹⁹.

The binding sites for ANP have been detected in various brain regions of animal and human species²⁰. In mammalian species, the highest concentration of all NPRs were found in the hypothalamus. In summary, the expression patterns of NPRs in the brain seem to complement each other, with NPR-C having the highest concentrations in the CNS. As discussed in detail by Cao and Yang, most studies on the localization of NPRs in the CNS have focused on animal models¹⁶ and there is need for mapping of NPRs in the human CNS.

The expression of NPs in astroglial cells has been repeatedly reported. ANP-immunoreactive astrocytes have been found in canine brain and in human cerebral and cerebellar cortices. In human cerebellum, the most abundant form of ANP-immunoreactive astrocytes were found to be Bergman glia²¹. The expression of all NPs and their receptors were also detected in astrocytes and vascular structures of human retina²². It was shown that NPs are stored in vesicles of astrocytes and that their release occurs by calcium dependent exocytosis²³. Moreover, existing evidence suggests that NPRs are mainly localized in astroglia cells of various CNS regions. For example, NPs stimulated cGMP accumulation in cultured rat astrocytes with CNP being the strongest one; and astrocytes in diencephalon accumulated more cGMP than cortical astrocytes suggesting a region specific expression of NPRs²⁴. These findings suggests the potential roles of astroglia cells in physiological activities of NPs in the brain.

In summary, NPs and their receptors are present not only in the systemic circulation but also in the CNS. Interestingly, research suggests that the central and systemic NPs might function in a feedback loop, such that increased plasma NPs during volume expansion and cardiac wall stretch might down-regulate the NPRs in the brain. This notion is supported by animal studies showing that rats with myocardial infarction have significantly decreased

levels of central ANP in several brain regions, including the circumventricular organs²⁵. Since the circumventricular organs are outside the blood-brain barrier and have high density of NPRs, the concentration of NPs in this region is proportional to their receptor density and indicates the possibility of down-regulation of NPRs²⁵. Besides, the presence of NPRs in endothelial cells of cerebral micro-vessels have been previously reported²⁶ which might be another possible pathway of the communication between central and systemic NP systems. Alternatively, it has been also postulated that the central NPs might influence their systemic production/function by showing that lesion in the AV3V region (anterior ventral region of the third ventricle) of rats inhibits volume-induced increase in systemic ANP²⁷. Obviously, there is a need for future research to elucidate the cross-talk between central and systemic NPs.

Relevance of NPs to cognitive impairment

Cognitive impairment and its ultimate presentation; dementia is a complex medical condition that affects a considerable proportion of the elderly population²⁸. Increasing evidence suggests that multiple pathological pathways are responsible for development of cognitive impairment. Among them, A β deposition, tau protein abnormalities, neurovascular dysfunction, oxidative and inflammatory damage, synaptic failure and glia cell activation are commonly believed as the key features of cognitive impairment and dementia^{29, 30}. Nevertheless, to date there is no effective treatment for these devastating disorders. Given the abundance of NPs in the brain, numerous studies have attempted to delineate their roles in the physiology of the CNS. It was shown that NPs play key roles in the regulation of neurotransmitters release and re-uptake, synaptic transmission and plasticity, microglial cell activation, neuro-inflammation, neuroprotection and blood-brain barrier integrity. Since brain NPs regulate several functions that are disturbed during the course of cognitive impairment, their functional disturbances might be responsible for development of cognitive impairment. Below we discuss the relevance of NPs functions in the brain to cognitive impairment in a random order.

NPs, A β and Tau protein depositions in the CNS

Alzheimer disease (AD) is the most common type of dementia²⁹. The dominant hypothesis for AD pathogenesis is the A β hypothesis, stating that the deposition of A β in senile plaques of the extracellular brain tissues is the main cause of AD. The A β peptide is produced during β -amyloid precursor protein (APP) processing. The A β hypothesis was supported by the observations that the gene for the APP is localized on chromosome 21, and patients with Down syndrome (trisomy 21) commonly develop AD by the age of 40. The imbalance between production and clearance of A β peptides from the brain is believed to play essential roles in the pathology of AD. The accumulation of neurotoxic A β substances disturbs synaptic activity and neurotransmitters' function, which then might lead to memory loss and other clinical symptoms of cognitive impairment and AD³¹. Another leading hypothesis is the tau protein hypothesis, proposing tau protein abnormalities as the main initiators of AD. Hyperphosphorylation of tau protein leads to formation of neurofibrillary tangles, which disrupts the organization of microtubules and the cytoskeleton of the cells. This results in impairment of synaptic transport and thus impaired neuronal function³².

Recently, the results of the "Alzheimer's Disease Neuroimaging Initiative" have shown that higher circulating levels of BNP are associated with lower CSF A β 42 levels and higher t-tau/A β 42 ratios, with effect estimates comparable to the number of *APOE4* alleles³³. Earlier, in an attempt to identify CSF biomarkers for early identification of mild cognitive impairment and AD, it was reported that the CSF levels of N-terminal pro BNP (NTproBNP) are elevated in subjects with mild cognitive impairment in comparison to non-demented subjects. It was also shown that CSF levels of NTproBNP are positively correlated with tau, p-tau 181 and tau/A β 42 ratio³⁴. This might be explained by the findings that no BNP mRNA have been detected in the CNS, proposing the possible peripheral source of BNP in the CSF of subjects with cognitive impairment³⁵. Another study has suggested that ANP and A β share a common clearance pathway from the brain; and that the insulin-degrading enzyme is the possible mediator in this pathway. It was postulated that since ANP has a higher affinity for insulin-degrading enzyme than A β , higher ANP levels in the brain might influence the

clearance of A β protein from the CNS³⁶. This evidence, although still in their infancy, opens novel areas of research, that aim to identify the roles of NPs in formation of neurofibrillary tangles, senile plaques, and clearance of A β from the CNS of AD patients. The observed correlations need to be further studied to validate the prognostic value of NPs, in plasma and in CSF, in patients with mild cognitive impairment and AD. Although studies have mostly measured BNP or ANP, measuring CNP in the CNS and/or CSF of cognitively impaired subjects is of critical importance considering the widespread concentrations of this peptide in the CNS.

NPs and neurovascular dysfunction

Recently, it has become more appreciated that neurovascular dysfunction plays an important role in the pathophysiology of cognitive impairment which might occur years before its clinical onset³⁷. Amongst others, disruption in blood-brain barrier (BBB) function may result in impaired clearance of A β and other toxic substances from the brain, and consequently contribute to development and aggravation of AD³⁸. Accumulating evidence suggests the involvement of NPs in regulation of BBB and cerebral blood flow. Animal studies have detected specific binding sites for ANP and BNP in cerebral vasculature including brain capillary endothelial cells^{26,39}. It has been shown that ANP increases cGMP in rabbit and pig cerebral microvessels; and that CNP increases cGMP in primary cultured cerebral microvessels in a dose dependent manner suggesting the involvement of these peptides in modulation of the BBB⁴⁰. Furthermore, roles of NPs in regulation of water and brain electrolyte balance have been suggested in rats by showing that ANP decreased brain water and sodium in areas of brain edema using MRI techniques⁴¹; and intracerebroventricular administration of ANP decreased brain edema after hemorrhagic brain injury⁴². The existence of tight junctions between endothelial cells of CNS contributes to the functions of the BBB. The cytoplasmic proteins zonula occludens (ZO-1) is involved in forming the tight junction of BBB. Recently, it has been shown that CNP increases the permeability of BBB by altering the expression of ZO-1 *in vivo* and *in vitro* and this was proposed to have a cGMP dependent

mechanism. As such, CNP might play a critical role in permeability of the BBB, which might be beneficial in improving the transport and delivery of drugs to the CNS⁴³.

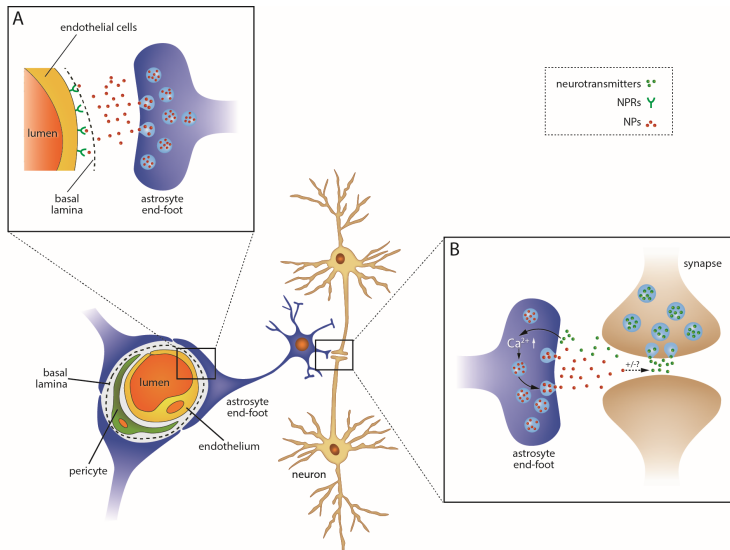


Figure 1. The interaction between astrocytes and NPs in regulation of brain physiology. The end-feet of astrocytes are in contact with several neuronal networks and at the same time with the cerebral blood vessels, hence regulating the function of both structures. **A:** The NPRs are located in endothelial cells of brain vasculature in various regions including choroid plexus. The release of NPs from astrocytes in response to neuronal function might lead to activation of NPRs. This in turn might increase the space between tight junctions of endothelium and facilitate transport of chemicals across the blood-brain barrier. NPs might also exert vasodilating functions on cerebral microvessels, in particular CNP. **B:** NPs are stored in vesicles in the astrocytes. Neuronal activity and neurotransmitters release increase the calcium concentrations in the astrocytes, which in turn stimulates the exocytosis release of NPs from astrocytes in the extracellular space. NPs then might regulate the action of several neurotransmitters by inhibiting or stimulating their release and re-uptake. In this way, neurotransmitters and NPs might function in a feed-back loop.

NPs might exert modulatory functions on brain vasculature and BBB via glia cells, in particular astrocytes. The end-feet of astrocytes is in contact with the synaptic membrane of neurons and blood vessels at the same time. Neuronal activity might increase calcium concentrations

in astrocytes and hence increase exocytosis of NPs⁴⁴, which in turn might affect permeability of BBB and/or vascular tones through stimulation of NPRs on endothelial cells of brain vessels (Figure 1). On the other hand, the BBB itself might also play role in clearance of NPs from the CNS and regulate their brain concentrations. Ito and colleagues have identified the expression of NPR-A and NPR-C in rat brain capillaries and demonstrated that NPR-C mediates the efflux transport of ANP from brain to blood, suggesting that BBB efflux transport is involved in elimination of NPs from the brain⁴⁵.

NPs and neuro-inflammation

Animal and clinical studies strongly suggest the involvement of neuro-inflammation in the pathophysiology of dementia and AD³⁰. Several studies have shown that the concentration of inflammatory markers such as the inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor α (TNF- α) is increased in the brain of AD patients³². TNF- α in the CNS exerts its action by inhibiting the transport of A β from brain to periphery. Consequently, increased TNF- α concentrations might increase the levels of A β in brain. Similarly, IL-6 may result in increased A β 42 production by affecting APP. Furthermore, activation of microglia cells during the course of AD has been repeatedly reported. Microglia cells in the CNS are activated during brain damage. Increased activity of activated microglia cells may result in enhanced production of cytokines, reactive oxygen and nitrogen species that may have unfavorable effects in the CNS. A β can also stimulate microglial cells to produce neurotoxic and inflammatory factors³². It is proposed that the inflammatory response of microglia cells is mediated via the cGMP pathways. In line with this, intraperitoneal injection of a cGMP-phosphodiesterase inhibitor – zaprinast – decreased the activation of microglia/macrophage cells in mouse models with cortical cryoinjury and lowered oxidative stress and decelerated neurodegeneration⁴⁶.

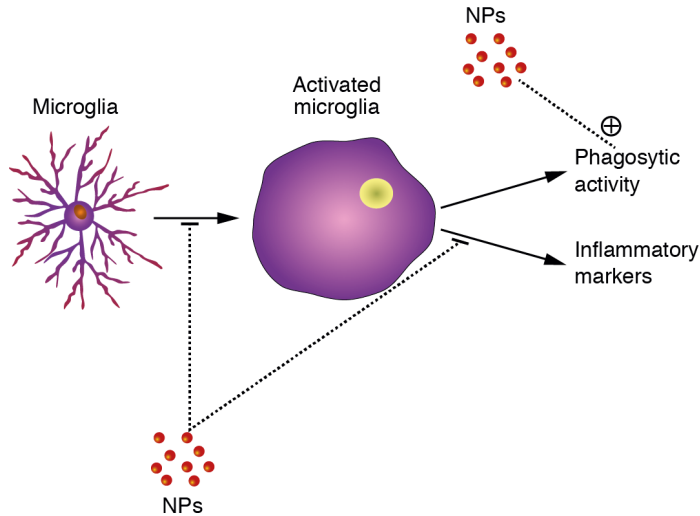


Figure 2. Anti-inflammatory actions of natriuretic peptides (NPs) in the brain. NPs might act on several pathways to reduce inflammation in the brain, in particular through their effects on microglia cells. They might inhibit the transformation of microglia cells to activated microglia cells. NPs might also directly inhibit the production of inflammatory markers or increase the phagocytic activity of microglia cells in the central nervous system

Existing evidence supports the involvement of NPs in regulation of inflammatory processes in the CNS, in particular of ANP. It was shown that in lipopolysaccharide (LPS) activated macrophages, ANP binds to NPR-A and inhibits production of nitrite and IL-1 β through inhibition of the pro-inflammatory transcription factors of nuclear factor κ B and activator protein-1, suggesting the involvement of ANP-NPR-A system in the regulation of neuro-inflammation⁴⁷. Intravenous administration of human recombinant BNP (nesiritide) to mouse models with traumatic brain injury and intracerebral hemorrhage reduced microglia cell activation and inflammatory markers TNF- α and IL-6⁴⁸. Boran and colleagues have shown that ANP decreases the LPS-induced expression of inflammatory genes, namely nitric oxide synthase Type 2 and TNF- α in rat microglia cells. ANP could also increase the phagocytic activity of microglia cells in primary and hippocampal organotypic cultures of rat. ANP might exert favorable effects on damaged brain tissue and suppresses the expression of anti-

inflammatory genes⁴⁹. These data suggest that the regulatory actions of NPs on inflammatory processes in the CNS is at the level of microglia cells. NPs may exert their anti-inflammatory actions by reducing the activation of microglia cells, inhibiting the secretion of pro-inflammatory markers and stimulating phagocyte activity of microglia cells (Figure 2). Together, evidence points toward the importance of NPs in regulation of inflammatory processes in the CNS and their potential value in management of cognitive impairment and dementia as anti-inflammatory substances.

NPs and neuroprotection

Several studies have provided evidence on neuroprotective effects of NPs. Cortical spreading depression (CSD) – a spreading wave of electrical hyperactivity in the brain which is followed by subsequent inhibition of electrical activities – is known to be protective against cerebral ischemia. It was shown that cortical expression of ANP mRNA is increased in rats preconditioned with a CSD episode and that this is accompanied by increasing cGMP levels, suggesting the involvement of an ANP-cGMP pathway in neuroprotective effects of NPs⁵⁰. ANP and BNP could suppress the apoptotic fragmentation of DNA in cultured PC12 cells and improve their survival by prolonging the elevation of cGMP levels⁵¹. The same group has shown that pretreatment with ANP protects NG108-15 cells, a cholinergic-neuron-like cell line, against nitric oxide induced apoptosis by increasing cGMP levels. The authors hypothesized that the neuroprotective effect of NPs via elevation of cGMP might be protective against neurodegenerative disorders in which nitric oxide is responsible for neuronal apoptosis⁵². Furthermore, Kuribayashi and colleagues showed neuroprotective effect of ANP in rat retinal neurons. They have demonstrated that ANP-NPR-A pathway is protective against N-methyl-D-aspartate-induced neurotoxicity possibly by activation of dopamine D1 receptors⁵³. CNP was also shown to protect rat retinal ganglion cells against apoptotic damage both *in vitro* and *in vivo*⁵⁴.

Using immunohistochemistry methods, it has been shown that the number of ANP-immunoreactive glial cells is increased in the white matter around brain infarcts⁵⁵.

Intravenous administration of BNP increased cerebral blood flow and reduced inflammatory markers (TNF- α and IL-6) and neuronal degeneration in mouse models⁴⁸. In line with this, ANP decreased sodium and water accumulation and reduced brain edema after cerebral ischemia and intracerebral hemorrhage in rats⁴². These findings suggest that the neuroprotective effects of NPs might be mediated via regulation of cerebral blood flow and NPs might possess protective effect on brain neurovascular structures, although further studies are warranted to explore their precise mechanisms.

NPs and synaptic regulation

Synaptic alterations and synaptic failure have been proposed as possible pathophysiological mechanisms behind AD and other types of dementia⁵⁶. In AD, A β accumulation leads to synaptic disassociation, which in turn may disturb neurotransmitters and synaptic functions and hence the presence of clinical symptoms such as memory impairment. It is suggested that the disturbances in synaptic function begin in the hippocampal areas prior to neurodegeneration⁵⁷. In line with this, evidence suggests that NPs might control the action of neurotransmitters including noradrenalin, dopamine and glycine. It has been shown that ANP negatively regulates the release of noradrenalin in slices of rat hypothalamus⁵⁸ and increases the uptake of noradrenalin in rat hypothalamus and medulla oblongata⁵⁹. Furthermore, intracerebroventricular injection of CNP inhibits cocaine-induced release of dopamine in caudate putamen, suggesting a regulatory role on dopaminergic neurons⁶⁰. Recently, Maeda and colleagues showed that ANP directly acts on the glycinergic presynaptic nerve terminals and inhibits the release of glycine in spinal cord sensory circuits of rats⁶¹.

NPs may also be involved in the regulation of synaptic plasticity and processing of information. For example, application of CNP to hippocampal slices of rat decreased population spike amplitude after high frequency stimulation and affected long-term potentiation⁶². CNP could decrease hippocampal network oscillations that are related to short- and long-term memory and the *in vitro* results from the same group demonstrated that CNP is involved in the regulation of bidirectional plasticity in hippocampal area CA1⁶³.

Consistently, other studies reported that CNP influences anxiety, arousal, learning and memory processes in rats. It was also shown that treatment with receptor blockers of dopamine, acetylcholine and nitric oxide inhibited learning effects of CNP in rats⁶⁴.

Apart from the effects of NPs on neurotransmitter release and uptake, neurotransmitters themselves might also regulate the release of NPs from astrocyte cells. Although astrocytes have long been known for their supporting actions on neighboring neuronal cells, growing evidence indicates that they also release several chemicals known as gliotransmitters in response to various physiological and/or pathological stimuli. Interestingly, it has been shown that NPs are among gliotransmitters secreted from astrocytes, and this release was shown to be calcium dependent. Calcium fluctuations in astrocyte in response to neurotransmitters might stimulate exocytosis release of NPs. In this way, NPs might play important roles in processing of information through neuro-glia interactions²³ (Figure 1).

NPs and anxiety

Anxiety has been implicated in cognitive impairment. It has been shown that older subjects with cognitive impairment have elevated anxiety levels, and increased anxiety has been related to poor cognitive function as well as accelerated future cognitive decline. Different pathological mechanisms have been proposed to play a role in the relation between anxiety and cognitive impairment, including alterations in neurotransmitter functions and availability, brain structures and HPA-axis activity⁶⁵. Amongst others, it has been suggested that chronic activation of the HPA-axis might reduce the hippocampal volume and contribute to cognitive decline. Furthermore, accumulation of lifetime stress has been hypothesized to reduce the feedback inhibition of the HPA-axis and therefore lead to hypercortisolism, which might in turn accelerate the ageing process⁶⁶. Interestingly, it has been shown that increased anxiety and A β levels are correlated with decreased memory function in healthy older adults. In this study, subjects with increased A β and anxiety symptoms had accelerated decline in cognitive domains that are controlled by temporal and prefrontal cortex of the brain⁶⁷.

It is suggested that NPs have modulatory effects on anxiety disorders by affecting the HPA axis. It has been shown that ANP inhibits the release of corticotropin releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) and directly inhibits cortisol release⁶⁸. Intracerebroventricular administration of ANP and CNP decreased anxiety related behaviors in rats^{69, 70}, and the inhibitory effect of CNP on anxiety was shown to be dose dependent⁷¹. In an attempt to test the inhibitory role of brain NPs on the HPA-axis in humans, ANP was administered intranasally to reach the brain directly in 18 male subjects. ANP was able to strongly inhibit hypoglycemia induced release of ACTH and cortisol, suggesting inhibition of the HPA-axis in hypothalamus⁶⁶. Together these data suggest potential beneficial effect of central NPs on anxiety related symptoms that might provide more feasible strategies to manage cognitive impairment in older adults.

NPs and memory

CNP have been shown to participate in regulation of learning and memory. Passive avoidance memory is a type of conditioning during which the subject learns to avoid certain behaviors in order to prevent the occurrence of aversive stimuli. Telegdy and colleagues have shown that intracerebroventricular injection of CNP improved learning when injected 30 minutes before learning trial, and consolidation of passive avoidance memory when injected 30 minutes after learning trial. They have also shown that administration of ANP and BNP to the lateral brain ventricle improved passive and active avoidance learning behaviors^{64, 72}. Moreover, the relation between CNP and neuroplasticity has been studied using electrophysiological methods. As discussed previously, CNP was able to regulate hippocampal network oscillations which are responsible for storage of information and consolidation of memory; regulate the magnitude of long-term potentiation and long-term-depression; and was shown to be involved in the regulation of bidirectional plasticity in hippocampal slices^{62, 63}. Because the hippocampus is linked to memory processes and CNP and its receptors are abundantly located in hippocampal areas, it can be hypothesized that CNP contributes to the regulation of memory and learning behaviors, although further studies are needed to assess the direct relation of CNP with memory functions.

NPs and fluid homeostasis in the CNS

One of the pathological features of AD is that the volume of CSF is increased due to atrophic loss of brain mass. However, the ability of CSF to renew itself - CSF turnover - is reduced which jeopardizes the clearance of harmful metabolites such as A β from the brain. It has been shown that during ageing and AD the turnover rate of CSF decreases by 3 to 4 times. This altered fluid homeostasis in the CNS during neurodegenerative disorders might negatively affect neuronal processes and cognitive function⁷³.

In the periphery, NPs are secreted from the heart in response to volume overload, which results in increased natriuresis, diuresis and decreased blood pressure. Evidence suggests that these peptides might have similar functions in the CNS that is regulation of CNS fluid homeostasis. NPs and their receptors are found in the choroid plexus and circumventricular organs, which are the sites of CSF production. As a result, it is possible that they regulate fluid homeostasis in the CNS by adjusting the production of CSF in the choroid plexus. Indeed, it has been shown that ANP regulates intracranial pressure by reducing CSF formation⁷⁴. Furthermore, Yamasaki and colleagues showed that intracranial hypertension was positively related to increased CSF levels of ANP in neurological patients, while this was not accompanied by raised circulating levels of ANP⁷⁵. Schouten and colleagues found that CSF N-terminal pro CNP (NT-proCNP) and CNP are inversely related to plasma concentration of CNP, which suggests that CSF levels of CNP might be regulated differently than their systemic concentrations⁷⁶. Interestingly, Mori and colleagues have shown that extraluminal administration of CNP produces a dose dependent vasodilatory effect on cerebral arteriole of rats⁷⁷. The vasodilatory action of CNP was proposed in patients with subarachnoid hemorrhage (SAH) as well. It was shown that CSF levels of CNP are increased one day after SAH, whereas plasma levels of CNP were not changed⁷⁸. Recently, it has been shown that elevated systemic concentrations of CNP in pregnant sheep did not increase CNP levels in the CSF⁷⁹. Together, these evidence supports the hypothesis that NPs in the brain contribute to the production and flow of CSF within the CNS, which is independent of their systemic concentrations. In line with this, one study examined the effect of elevated systemic levels

of NPs on their central concentrations. They found that in ovine, pacing-induced heart failure was associated with lower central levels of BNP, in particular in pituitary region⁸⁰. Furthermore, the inverse relation between CSF and circulating levels of NPs makes the central NPs as potential novel targets for diagnosis of CNS disorders. In this setting, it has been shown that CSF levels of CNP are decreased in patients with Parkinson's disease and lower CSF levels of CNP at baseline were related to worse functional outcomes¹. However, more studies are needed to clarify the specific role of CSF NPs in neurodegenerative disorders.

Plasma NPs and brain structural integrity

Despite the wealth of evidence from animal studies, limited human data is available on the roles of brain NPs in the structural and functional integrity of the brain. Several studies reported that higher circulating levels of BNP and its precursor NTproBNP are associated with impaired cognition. Elevated plasma levels of BNP have been associated with increased risk of cerebrovascular events, structural brain changes and subclinical brain damages such as with matter hyper-intensities⁴. The Framingham offspring study of 3127 stroke-free individuals showed that high plasma BNP levels increased the risk of stroke or transient ischemic attack and improved the risk prediction of the Framingham Stroke Risk Profile, independent of blood pressure, cardiac and renal diseases⁸¹. The results of the Atherosclerosis Risk in Communities study showed that higher NTproBNP plasma levels were associated with silent brain infarcts and white matter lesions independent of cardiovascular risk factors⁸². Furthermore, recently we have shown that higher serum NTproBNP levels are associated with lower brain volume, cognitive impairment and depression independent of cardiovascular risk factors and cardiac output⁴. Shibazaki and colleagues have shown that patients with intracerebral hemorrhage have higher plasma BNP levels; and plasma BNP was related with intraventricular extension and resulting hydrocephalus⁸³. The available evidence implies that low CNS and high peripheral concentration of NPs are linked with structural and

functional alterations in the brain. Higher NPs in CNS are crucial for maintenance of homeostasis in the brain while elevated systemic concentration of NPs might suppress central NPs and their receptors⁸⁰.

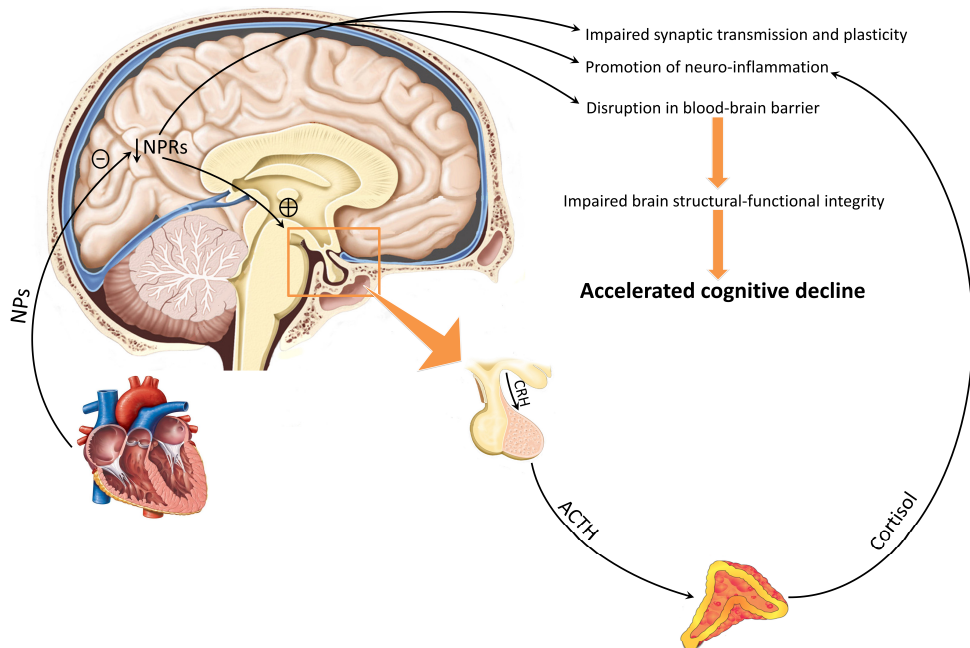


Figure 3. The potential role of natriuretic peptides (NPs) and their receptors (NPRs) in cognitive impairment. High systemic levels of NPs may lead to down-regulation of NPRs in the brain which in turn would result in dysregulation of synaptic transmission and plasticity, promotion of neuro-inflammation and disruption of the blood brain barrier. These brain deficiencies are responsible for impaired structural and functional integrity of the brain that ultimately accelerates cognitive decline. Abbreviations: CRH: corticotropin releasing hormone, ACTH: adrenocorticotropic hormone

Summary and conclusion

Finding effective disease modifying strategies for cognitive impairment still represents an unmet goal. There is an increasing body of evidence showing that disturbances in various

pathways act in concert to initiate and promote neuronal injuries, cell death and functional impairments in the neuronal networks in the brain of cognitively impaired patients. This extraordinary level of complexity in the pathophysiology of cognitive impairment has been marked as a possible reason for failure of the recent trials targeting specific pathologies. Hence, further attention needs to be paid to strategies that can identify subjects at risk in early stages and also modify the course of cognitive decline by acting on various key pathologic pathways. Although various mechanisms for cognitive impairment have been proposed, neurovascular dysfunction, glial cell activation, oxidative and inflammatory damage and synaptic failure are among the key features of cognitive impairment. Therefore, disease modifying treatments that will be effective on multiple pathways can potentially decelerate the pace of cognitive decline. In line with this, we suggest that NPs play essential roles in multiple pathways including regulation of neuro-inflammation, synaptic transmission, CNS fluid homeostasis and modulation of systemic and CNS stress response. Animal studies have shown that activation of the brain NPRs improves memory and learning behavior. Furthermore, elevated plasma NPs might down-regulate the expression of NPRs in the CNS. Hence, we hypothesize that reduced central action of NPs in the brain, possibly as a result of their elevated systemic levels, might lead to impairment in several key physiological functions of the brain and disturb the integrity of the CNS, which might ultimately put subjects at higher risk of accelerated cognitive decline. Furthermore, reduced central action of NPs in the brain might increase the production of stress hormones of the HPA axis including CRH, ACTH and cortisol. This might alter the stress response of brain to various stimuli and lead to emotional impairments including anxiety. Elevated circulating cortisol levels, on the other hand, might accelerate neuro-inflammation and exaggerate the functional impairments in the CNS (Figure 3). Yet, future large-sample studies are needed to investigate (i) the function of NPs in the CNS in subjects with and without neurological disorders, (ii) the interaction between systemic NPs and their CNS levels to identify if the two pathways in the periphery and the CNS function separately or in a feed-back loop fashion, and (iii) the relation between CSF levels of NPs in patients with and without AD and their influence on future clinical outcomes. Among three members of NPs family, CNP seems to

be the most promising target given the abundance of this peptide and its receptors in the CNS and the specific role of CNP in the CNS needs to be further explored. Available evidence suggests that NPs are important regulators of overall integrity of the brain, and might represent novel targets in management of subjects with cognitive impairments.

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