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CENTRAL NERVOUS EFFECTS OF C-TYPE NATRIURETIC PEPTIDE AND NUCLEAR FACTOR KAPPAB; IMPLICATIONS IN CARDIOVASCULAR STRESS

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Abstract

Hypertension is a multifactorial and chronic disorder of elevated blood pressure. Persistent hypertension is deleterious for humans and may cause morbid changes in the organs e.g heart, kidneys, brain and the eyes. Natriuretic peptides i.e atrial, brain and C-type are secreted by the heart and are synthesized in other parts of the body. CNP is present in many discrete regions of the central nervous system (CNS). In this study, the effect of natriuretic peptides on memory and cognition, plasticity and behaviour are evaluated and reviewed. In this review the focus is on the C-type natriuretic peptide and its interaction with the nuclear factor kappa B (NFkappaB) in the central nervous system and implications in conditions of cardiovascular stress.

Introduction

The natriuretic peptide (NP) family is comprised basically of three peptides i.e atrial NP, brain NP, and c-type NP (CNP). These peptides play diverse physiological roles (1-2) by binding to one of two receptors: NP receptor (NPR)-A for atrial NP and brain NP or NPR-B i.e for CNP, both of which mediate signal ling through the guanylyl cyclase-cyclic GMP (cGMP) pathway (3) as depicted in Fig.1. Amongst the physiological systems involving NPs are those controlling the circulating blood volume, vascular tone, electrolyte balance, skeletal growth, and body energy expenditure (4). In addition to actions in peripheral tissues, NPs are present in brain (5). ANP is a 28 amino acid peptide with a ringed structure formed by intramolecular disulfide linkages. It is synthesized and secreted by the cardiac atria. The ANP gene in humans is located on the short arm of chromosome 1 (6). ANP is synthesized as a 151 amino acid preprohormone (preproANP) and is stored in atrial myocytes as a 126 amino acid prohormone (proANP). CNP, which was first isolated from porcine brain in 1990, consists of 22 amino acids (7). The ring structure of CNP is highly homologous with ANP and BNP but uniquely lacks the carboxy-terminal extension. The structure of CNP is almost identical among species. PreproCNP, comprising 126 amino acids, after cleavage of the first 23 amino acids is converted to proCNP, which is further processed to CNP-53 and/or CNP the potencies of which are essentially similar (8) CNP is distributed throughout the brain in rats and humans and its concentration is 10-fold higher than ANP and BNP in the cerebrospinal fluid.

The CNP works as an endogenous inhibitor of vascular angiotensin-converting enzyme activity (9). Angiotensin II induces collagen production in culture cells suggesting enhanced vascular stiffness (10). Angiotensin-II increases pulse wave velocity in healthy human indicating an increase in arterial stiffness (11). These studies along with the findings of the present study suggest that the reduced level of CNP as has been shown seen in Isolated systolic hypertension might lead to over-activity of ACE and subsequently abnormal arterial wall stiffness leading to increased systolic hypertension. CNP appears to be more rapidly hydrolysed by neutral endopeptidase than the other natriuretic peptides, (12) thus, endopeptidase inhibition may be a potential therapeutic intervention by enabling beneficial manipulation of natriuretic peptide levels thereby preserving the physiological role of CNP in ISH patients.

C-type natriuretic in discrete brain sites

The natriuretic peptide CNP and its receptor NPR-B are concentrated in the ARC (13), raise the possibility that CNP-containing ARC neurons synapse onto and activate adjacent POMC neurons. Alternatively, CNP neurons could conceivably activate POMC cells via an indirect mechanism involving an intermediary neuronal subpopulation (14). These untested possibilities are of potential interest because, possibly the anorectic effects of both leptin and serotonin may also be modulated. Of the natriuretic peptides, CNP is the most abundant in the CNS and exhibits the highest concentration of this family in human cerebrospinal fluid (15). Furthermore, both CNP

messenger ribonucleic acid its mRNA molecules and CNP receptors (natriuretic peptide receptor B; NPR-B) have been discovered extensively throughout the brain and spinal cord (16). CNP is a multitasking hormone, with various roles throughout the body, and within the nervous system (17). Much of the work to date on the role of in the central nervous system (CNS) has investigated this neuropeptide at the level of neurophysiology.

C-type natriuretic peptide and its biochemistry

Evolutionary studies indicate that ANP (Atrial) and BNP (B-type) have evolved from CNP (17). Both ANP and BNP bind to natriuretic peptide receptor A (NPR-A), whereas CNP has low affinity for NPR-A and is the sole ligand for NPR-B. All three peptides bind to the C receptor (NPR-C), which acts by internalising and degrading these intracellular peptides (18). CNP is synthesized in the body from a 103 amino acid pro-hormone (proCNP) peptide which is cleaved intracellularly to release the biologically active peptide (CNP-53) and a apparently biologically not much active amino-terminal fragment (NTproCNP) which is secreted in equimolar quantities to CNP (22). CNP-53 is the main bioactive form in tissues, including the brain, but further cleavage results in a smaller bioactive form (CNP-22) found at very low levels in systemic circulation (19). In addition to uptake by NPR-C and the intra-cellular degradation, CNP is also degraded by the action of at least two other enzymes – neprilysin (19,20) and Insulin-degrading enzyme (17). The combined actions of proteolysis and receptor clearance result in a relatively short half-life for CNP-22 in blood plasma, which in humans is approximately two to three minutes (21). The half-life of CNP-53 is not exactly known, but is likely to be longer than CNP-22. CNP-53 has previously been successfully measured in ovine hypothalamus and pituitary with extraction times of 10 minutes (22) suggesting a half-life of at least this length of time. As NTproCNP is considered biologically inactive, measures of concentrations of this molecule alongside CNP allow stronger conclusions to be drawn regarding secretion of CNP as reflected by NTproCNP concentrations compared with degradative actions on the peptide which are assessed using the ratio of NT proCNP to CNP concentrations. ELISA based methods using specific laboratory kits are now available to estimate the levels of NTproCNP supposedly a biomarker for clinically critical conditions.

C-type natriuretic peptide and memory

There is considerable interest in research investigating CNP during tasks thought to reflect different types of memory. For example, with the possible connection of changes in CNP to Alzheimer's disease pathology due to its degradation by neprilysin, it would be of value to study CNP concentrations during tasks that represent other aspects of episodic memory. Severe deficits in episodic memory are characteristic of Alzheimer's disease (23) and thus, it would be of benefit to investigate CNP changes subsequent to a task with spatial components, thought to be better representative of episodic memory in animal models (e.g. Morris Water Maze, Radial-arm maze). The medial prefrontal cortex is generally thought to be responsible for processes associated with strategy memory encoding and retrieval (25,26). In terms of recognition it is thought to be more important for familiarity and recency than novelty discrimination. However, some studies indicate that CNP production in median prefrontal corted (mPFC) is increased during novel object discrimination. If this suggestion is correct that CNP is associated with modulation in plasticity processes, this result indicates an increase in the potential for plasticity in mPFC over repeated presentations of novel objects. The most likely explanation, given previous research disseminating the role of mPFC in recognition memory, is that as more objects are presented, more information must be encoded, and potentially retrieved in the future, requiring greater potential for LTP/LTD in this region. CNP-53 has previously been successfully measured in ovine hypothalamus and pituitary with extraction times of 10 minutes (27) suggesting a half-life of at least this length of time. Both the neprilysin and Insulin-degrading enzyme also degrade the amyloid-β protein, deposits of which form plaques in Alzheimer's disease (28). Interestingly, one recent study suggested that neprilysin deficiency facilitated learning and memory in aged mice with a knockout of the gene encoding the enzyme (23). The notion of neprilysin deficiency improving learning and memory in the context of propsed effects of CNP on mnemonic processes is intriguing. Whether the CNP turnover and its conversion to NTproCNP is enhanced during hypertension needs to be investigated. Is the conversion of preproCNP to NTproCNP causing any memory deficits or morphological changes in the cerebral vascularity leading to neurological deficits must be investigated.

Central nervous effects of C-type natriuretic peptides in hypertension

The three NPs i.e ANP, BNP, and CNP and their receptors are expressed in the brain, which implies a possible role for these peptides in brain function. Neurons of the circumventricular organs express receptors for the majority of the cardiovascular hormones (29), including NP receptors: NPR-A and NPR-B were found in the vascular organ of lamina terminalis, the subfornical organ, area postrema, and the choroid plexus. CNP is the most abundantly present natriuretic peptide in the brain (15) and its mRNA is expressed in the brain, suggesting that it acts as a neurotransmitter or neuromodulator rather than a cardiac hormone (20). Accordingly, the CNP-specific receptor – NPR-B is widely spread throughout the brain: NPR-B mRNA was detected in the cerebral cortex, the limbic area, preoptic-hypothalamic regions, motor nuclei, and the brainstem (14). A study performed on conscious sheep showed that CNP, but not ANP, decreased BP upon i.c.v. administration (30). CNP is a potent anxiogenic substance that acts by stimulating the HPA-axis. It is therefore that CNP antagonists were considered in anti-anxiety therapy (31). Studies conducted by this author at the Georgia Health sciences center, USA showed that CNP was a critical natriuretic peptide in the brain and heart of DOCA salt hypertensive rats which also exhibited a model of mild heart failure due to persistent hypertension. These observations were based on the effects on parameters like the blood pressure, heart rate and Guanylate cyclase activity. An interaction of CNP with ion channels in smooth muscle physiology is shown in Fig.2

NFkappa B in the central nervous system

Within the CNS, NF-κB signaling encompasses activation of preformed RelA and p50 containing dimers, which are cytoplasmically sequestered by inhibitory IκBα i.e the canonical pathway (32). Fast kinetics of canonical NF-κB is guaranteed by stimulus-dependent activation of the IκB kinase (IKK) complex leading to serine phosphorylation of IκBα by IKK-β subunits, its proteosomal degradation, and the nuclear translocation and DNA binding of RelA/ p50 (33). Activity assays using κB-dependent expression of the reporter enzyme β-galactosidase (β-gal) reveal a constitutive activation of NF-κB in neurons of the developing and, at least in part, of the mature CNS (34). NF-κB transduces signals related to peripheral cell damage to the neuronal soma/nucleus (35). Such intracellular redistribution of NF-κB was first demonstrated using enhanced green fluorescence protein-tagged RelA fusion proteins (EGFP-RelA), where stimulation of hippocampal neurons with glutamate induces retrograde transport of RelA from synapses back to the nucleus (36). *In vitro* studies have emphasized a neuritogenic potential of NF-κB in developing neurons. Thereby, NF-κB signaling either stimulates or inhibits neurite outgrowth in cultured superior cervical ganglion sympathetic neurons or nodose ganglion sensory neurons depending on the cell type's specific phosphorylation status (Ser536) of RelA (37).

NFkappa B and CNP interaction in memory

Experimental studies conducted by Tyagi *et al* (38) suggest that NF kappa B inhibition leads to attenuation of CNP mediated effects on memory function in rats. This can be attributed to the decrease in cGMP mediated CREB phosphorylation, and supports the work done by Kaltschmidt et al (39). Thus NF kappa B seems to play a major role in CNP and associated Guanylate cyclase mediated increase in cGMP levels. Much more extensive work involving specific sites of the brain needs to be conducted. In the cardiovascular system, removal of NO an important free radical for activating the cytosolic cGMP was shown to prevent NF-κB subunit nitrosylation and association with the inhibitory factor IkB, thus enabling translocation of NF-κB subunits to the nucleus, which results in increased eNOS mRNA expression (40). A similar mechanism may be operative in human hypertension and metabolic syndrome as a response to increased ROS production and endogenous NOS inhibitors (41). In that case, NF-κB may represent an adaptive mechanism providing increased NO production during hypertensive and hypertrophic conditions when increased production of ROS and decreased NO generation can be assumed. A similar situation can be speculated in relation to the CNP and its signaling mechanisms, thus in concordant to our observations that both CNP and NFkappaB may play critical role in memory, cognition and neuronal plasticity, particularly in conditions of cardiovascular stress. The possibility of better proteomic evaluation of metabolites like the NTproCNP can be a useful biomarker in cardiovascular disorders (42).

Conclusion

Recent studies conducted on the role of natriuretic peptides and in particular the C-type natriuretic peptide suggest that CNP has a critical patho-physiological role in the brain, possibly as part of a neurological cascade responsible for neuroplasticity, learning and memory. While CNP is present in many discrete sites of the brain, there are few

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reports of its direct measurements in brain. It can be speculated that in cardiovascular stressful conditions like the hypertension, heart failure and cardiac arrhythmias, the CNP synthesis/expression and turnover may be enhanced and whether it could affect learning and memory processes as has been suggested by some studies for the NTproBNP needs further research studies. Based on the studies conducted by this author the NFkappaB is a likely candidate to enhance the effects of CNP and its inhibition may cause a reverse effect.

Fig.1 :

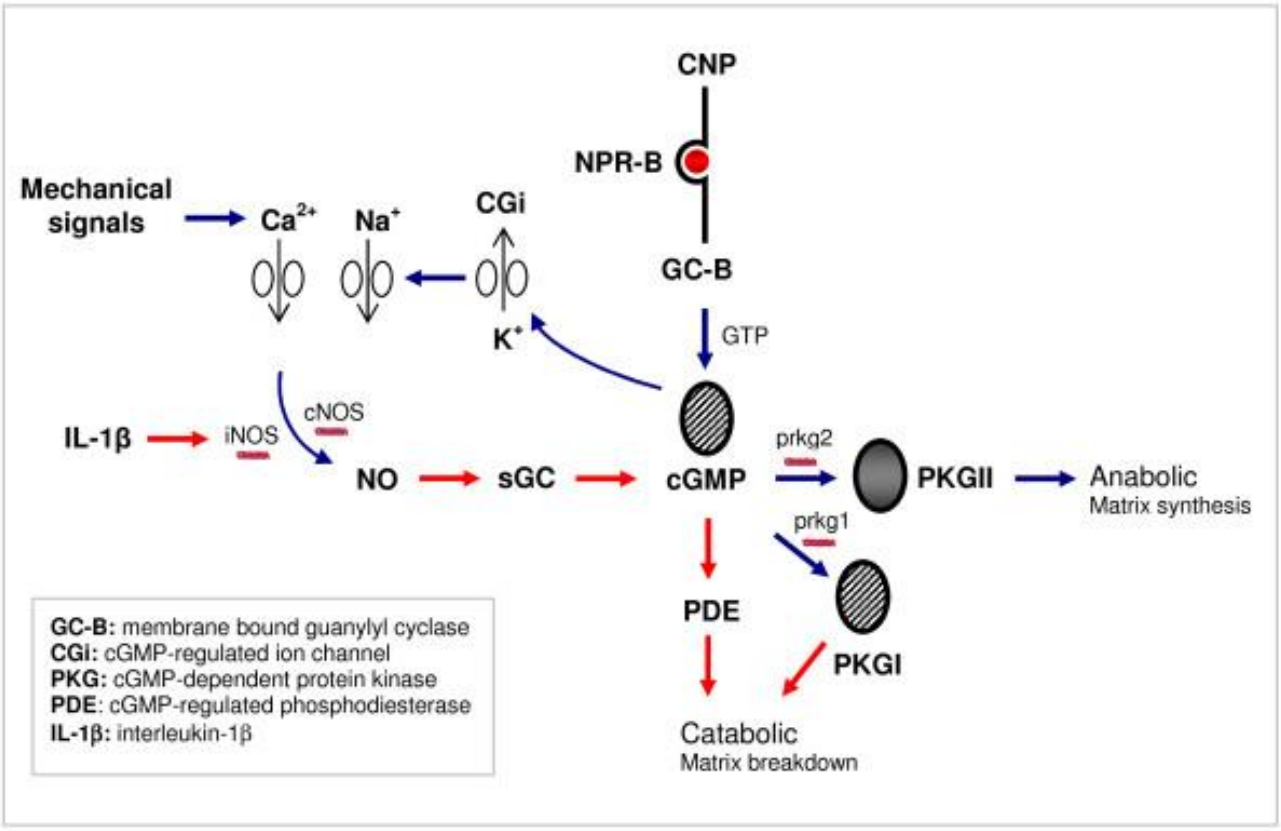

Fig.1 Courtesy: Ramachandran et al. Arthritis Res.Ther.2011, 13: R145

Fig.2

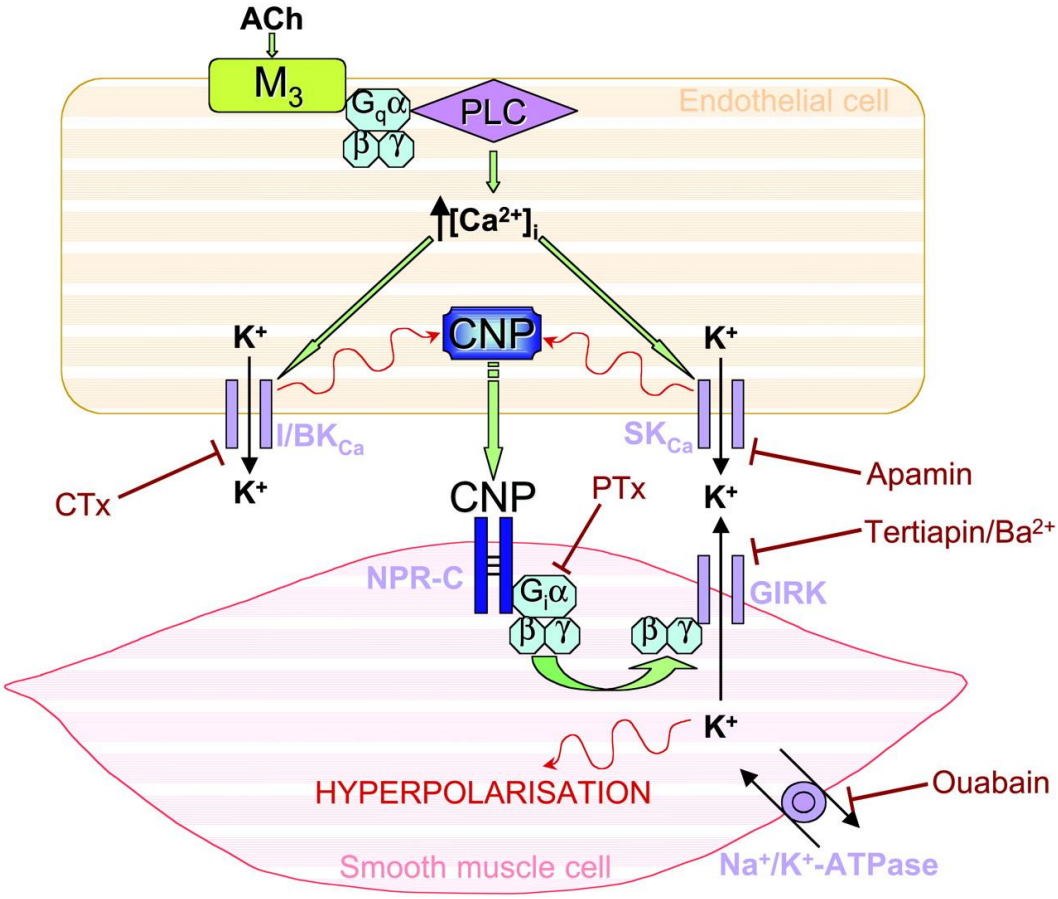

Fig.2 Courtesy: SD Chauhan et al PNAS, 2003, 100(3): 1426-1431

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