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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.

Contents

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 NPs in the nervous system is a rather unexplored area yet to be described.