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Mini Review

New aspects of the interactions between the cardiovascular nitric oxide system and natriuretic peptides

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ABSTRACT

Arterial blood pressure is regulated by a variety of endocrine, autocrine and neuronal systems. Natriuretic peptides and nitric oxide are important factors that exert synergistic vascular and cardiac actions and their activities are closely linked. The existence of a novel signal transduction mechanism involved in activation of nitric oxide synthase via natriuretic peptides is currently being explored. Since several cardiovascular disorders are associated with dysfunction of natriuretic peptides activity, selective modulation of the natriuretic peptides pathway represents an important therapeutic target. This review article highlights the current findings on cross-talk between natriuretic peptides and the nitric oxide system.

1. Introduction

Vascular tone and body fluid homeostasis, determinants of blood pressure, are regulated by a variety of endocrine, autocrine and neuronal factors. Natriuretic peptides (NPs) and nitric oxide (NO) are important factors that exert synergistic vascular and cardiac actions.

Since discovery of atrial natriuretic peptide (ANP) in 1981, several studies have investigated the role of NPs as a pathophysiological determinant of hypertension. ANP, B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) constitute the most studied members of the natriuretic peptide family [1]. ANP and BNP are mainly produced in the cardiac atria and ventricles. Both peptides are present in the circulation and directly influence blood pressure and body fluid homeostasis [2]. CNP is extensively distributed in the cardiovascular system, particularly in endothelial cells and cardiac myocytes [3].

The biological functions of NPs are mediated by two specific membrane-bound guanylyl cyclase (GC) receptors: natriuretic peptide receptor A and B (NPR-A and NPR-B, respectively) [4]. NPR-A responds to ANP and to a 10-fold lesser degree to BNP. NPR-B responds primarily to CNP [5]. NPR-A and NPR-B are expressed in the cardiac atria and ventricles, as well as in the aorta and peripheral vasculature, kidney, etc. [6–8]. There is a third receptor subtype, natriuretic peptide receptor C (NPR-C), that primarily controls NPs concentrations via receptor-mediated internalization and degradation, although many research groups have reported signaling functions for NPR-C as well [9].

On the other hand, NO was identified as a biological signaling molecule in the 1980s. NO is produced by NO synthase (NOS) and its three isoforms (eNOS, nNOS and iNOS) are expressed in many tissues, including endothelium, vascular smooth muscle, specific segments of the nephron and the heart [10,11]. It is widely known that NO binds soluble GC and increases cGMP levels.

The increase in cGMP induced by NO or NPs induces vascular relaxation, inhibits platelet aggregation and adhesion, reverts smooth muscle proliferation and participates in the regulation of renal homeostasis [6–8,12–14].

Given that a growing number of examples of the interplay between NPs and NO, and taking into account their effects on the regulation of cardiovascular functions, it is possible to postulate an interaction between both systems in the heart and vasculature. This review article highlights the current findings on the interaction between the mechanisms of action of these factors.

2. Vascular function and hypotensive effect

Considering that NPs and NO are vasoactive substances that induce hypotension through their vasorelaxant effects, we might also think that these two systems, which exhibit synergistic actions, may be related in some way or another.

Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; eNOS, endothelial nitric oxide synthase; GC, guanylyl cyclase; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; NPR-A, A-type natriuretic peptide receptor; NPR-B, B- type natriuretic peptide receptor; NPR-C, C-type natriuretic peptide receptor; NPs, Natriuretic peptides.

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On the basis of studies performed by means of endothelium denudation, in 1990 it was postulated that ANP-induced vasodilation was endothelium-independent. In this regard, Murohara et al. showed that denudation of the endothelium significantly sensitized relaxation to nitroglycerin but did not change relaxation to ANP [15]. The specific inhibition of soluble GC did not affect the relaxation or increase in cGMP elicited by ANP, which activates particulate GC [16]. Furthermore, a report on ANP-overexpressing transgenic mice and pro-ANP gene knockout mice (−/−) showed that, over a wide range of chronic ANP activity, neither the synthesis of ET-1, CNP and NO from the resistance vasculature nor their actions on the cardiovascular system were affected, thus indicating that the chronic effect of ANP on vascular resistance would not be mediated by the endothelium [17]. In this regard, Wei et al. showed that ANP and CNP mediated endothelium-independent relaxation of aortic rings in WKY and SHR rats [18].

In a later study, we found that the hypotensive effects of ANP were partially blunted when NO synthesis was inhibited. This was one of the first reports showing evidences that NO participates in the vascular effects of ANP. This fact was confirmed in aorta and arterioles by the NADPH-diaphorase histochemical method, a marker of isozyme-independent NOS. In this work, 8-Br-cGMP mimicked the effect of ANP GC-coupled natriuretic receptors, indicating that NPR-A and/or NPR-B could be involved in this ANP-induced NOS activation [19]. In accordance with these results, Nguyen et al. demonstrated that the relaxation response to ANP, BNP and CNP in the internal mammary artery and radial artery is primarily mediated by NPR-A/B and the cGMP pathway, and that it also involves activation of the NO system [20]. Additionally, the activation of NOS induced by ANP has been also demonstrated in aorta artery of young and adult SHR [21].

A number of studies showed that CNP induced vasorelaxation, while other authors found no vascular effects. We have reported that CNP induced a decrease of mean arterial pressure in normotensive rats [22]. This effect was also observed in dogs [23]. In contrast, other studies showed that CNP infusions induced a small increment in cGMP yet had no significant hemodynamic actions in humans [24].

Brunner et al. showed that relaxation of the coronary resistance vessels of the rat by CNP is partially mediated by the NO-cGMP pathway, supporting the existence of an endogenous link between soluble and particulate GCs in the control of vascular tone mediated by NPs [25].

It is well known that endothelial cells can reduce vascular tone by hyperpolarization of the underlying smooth muscle cells. In this regard, Simon et al. demonstrated that CNP hyperpolarizes pulmonary microvascular endothelial cells by activating large-conductance calcium-activated potassium channels mediated by the activation of NPR-B, PKG, eNOS, and sGC [26]. Moreover, our results showed that CNP activates eNOS by interacting with the NPR-C receptor in aorta artery of normotensive and hypertensive rats [22,27].

Van der Zandera et al. showed that in healthy men BNP increases cGMP and CNP plasma levels. They also demonstrated that BNP induces vasodilation not only by the opening of potassium channels, but also via stimulation of NO production [28]. In accordance with these findings, Zellner et al. demonstrated that BNP-induced vasodilation in coronary resistance arteries may be partially mediated by NO and prostaglandin release [29].

3. Heart

Three types of ANP receptors have been demonstrated in cardiac atria and ventricle [30]. Nachshon et al. defined an autoregulatory mechanism of ANP secretion by atrial myocytes in an autocrine/paracrine manner that involved NPR-C [31]. With regard to the actions of CNP in cardiac atria, Kim et al. attributed to CNP the role of negatively modulating ANP secretion in rat atria [32]. In addition, Lee et al. postulated that ANP release would be controlled by CNP via NPR-B-cGMP mediated signaling, which may in turn act via regulation of intracellular Ca^{2+} in rabbit atria [33].

Several studies support the hypothesis that NO may be involved in the regulation of ANP release in heart, but the results are controversial. NO may tonically inhibit the secretion of ANP in response to volume load in rat cardiac muscle, without changes in BNP secretion [34]. In contrast, both L-arginine as well as L-NAME (NOS inhibitor) had no effects on basal ANP secretion in the perfused rat heart [35]. Taking in account our *in vivo* and *in vitro* results showing that ANP and CNP activate NOS via NPR-C in atria, we could think that the activation of the NO system induced by NPs would participate in the mechanism involved in local regulation of the synthesis and/or secretion of ANP [22,36].

With respect to cardiac ventricle, several authors have reported negative, positive or no inotropic effects for PNs in different myocardial preparations and several species [37,38]. In *in vitro* studies it was demonstrated that low and moderate concentrations of ANP have a positive inotropic effect [39]. With respect to the NO system, Gyurko et al. provided evidence that eNOS activation attenuates systolic contractility response in intact animals and in the isolated Langendorff heart preparation. They also suggested that NO appears to regulate baseline ventricular relaxation in conjunction with ANP [40]. While *in vivo* and *in vitro* data indicate that, under basal conditions, cardiac function is normal in an eNOS knockout mouse model, suggesting that NO would only play a minor role in basal cardiac function, in beta-adrenergic stimulation conditions eNOS would mediate the negative inotropic effect [41]. Taking into account these contrasting inotropic effects of ANP and NO, we consider that there are no evidences to support that NO is involved in the inotropic effect of ANP.

CNP has a biphasic effect: a positive inotropic effect in the first stage and then a negative inotropic effect in isolated NPR-A deficient-mouse heart [42]. In addition, Brady et al. showed that the magnitude of the effect of CNP on contraction is similar to the effect reported for NO [43]. Interestingly, the reduction in contraction amplitude was associated with an increase in intracellular cGMP levels [44]. These results suggest that a cross-talk between both systems, NO-cGMP and CNP-cGMP, could participate in the regulation of cardiac contractility. Taking into account these findings and our results demonstrating that CNP activates NOS via NPR-C, we suggest that the increase in NO production induced by CNP could be the mechanism that would mediate the negative inotropic effect of this peptide [22].

Recent studies have revealed that cGMP plays a central role in the downstream signaling pathways mediating the cardiac antihypertrophic effects of NO [44]. In addition, mice carrying genetic deletion of GC-A, as well as a disruption of the NPR-A gene, develop cardiac hypertrophy and hypertension [46,47]. In this regard, taking into account our results, the antihypertrophic actions of ANP appear to be the result of two different pathways: the increase in cGMP via NPR-A-coupled to GC-A and the activation of NOS via NPR-C, with the ensuing NO increase.

With respect to CNP antiproliferative effects, Tokudome et al. have shown that CNP inhibits cardiomyocyte hypertrophy in a cGMP-dependent mechanism [45]. In this regard, our results suggest that the increase in cGMP through the activation of NOS could explain the inhibition of proliferation induced by CNP [27].

There are few data on BNP-NO interaction and its antihypertrophic effects. Wang et al. suggest that BNP exerts antihypertrophic actions on cardiomyocytes, which are partially attributed to induction of iNOS-derived NO [48]. Other authors found that BNP treatment increased NO synthesis in rat myocardium and remarkably reduced the infarct size of ischemia–reperfusion myocardium [49].