Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

Mini Review

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

María A. Costa *, Cristina T. Arranz

Cátedra de Fisiología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, IQUIMEFA-CONICET, Junín 956, piso 7, 1113 Ciudad de Buenos Aires, Argentina

ARTICLE INFO

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.

© 2011 Elsevier Inc. All rights reserved.

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.

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].

4. Signaling pathway

The relation between NPs and the activation of NOS has been demonstrated in different tissues and species, and the signaling pathways implicated in this interaction have also been investigated, identifying the natriuretic receptors and NOS isoforms involved.

The activation of cardiovascular NOS induced by ANP and CNP involves the eNOS isoform, the inhibition of iNOS and nNOS does not affect NOS stimulation mediated by these peptides. When we analyzed whether NOS activation via ANP or CNP involved an increase in the expression of the enzyme, we observed that NOS stimulation induced by both peptides was not associated with modifications in eNOS protein expression [50]. By contrast, with respect to BNP, it has been demonstrated that this peptide increases iNOS and eNOS expression in cardiomyocytes cultures and rat myocardium, respectively [48,49].

The natriuretic receptor type and the signaling cascade involved in NOS activation induced by ANP still remain to be completely elucidated. Our results demonstrated that both ANP and cANP (4–23) (NPR-C receptor agonist) increased NOS activity in cardiac ventricle and atria and in aorta artery [51]. These findings are in accordance with the studies performed by other authors that showed that both ANP and cANP (4–23) activate NOS and stimulate NO formation in gastric smooth muscle cells and in human proximal tubular cells [52,53]. The fact that cANP (4–23) induced an increase in cardiovascular NOS activity would indicate that the NPR-C receptor is involved in NOS activation induced by ANP.

The stimulation of NOS induced by ANP and cANP (4–23) was similar in cardiac atria, suggesting that NPR-C would be the unique receptor involved in the stimulation of NOS via ANP in this tissue.

In cardiac ventricle and aorta artery, ANP provoked a more marked increase in NOS activity than cANP (4–23), and NPR-A/B blockade blunted this effect, indicating that NPR-A and/or NPR-B may also be involved in NOS stimulation induced by ANP [50]. The fact that physiological concentrations of ANP activate GC-A via NPR-A but not GC-B via NPR-B would indicate that NPR-A is the receptor involved in NOS activation by ANP [5,52,54]. The participation of the cGMP/PKG pathway in the regulation of NOS activation via ANP was demonstrated in previous reports [50].

Moreover, we observed that NOS activity stimulated by ANP and cANP (4–23) was abolished when calmodulin and/or Ca^{2+} influx was blocked, suggesting that the signaling cascade was triggered by agonist-induced Ca^{2+} influx and mediated by Ca^{2+}/calmodulin-dependent NOS [51]. However, NPR-C participation in this ANP action cannot be discarded since NPR-C has a short cytoplasmatic tail, whose functions include both a Gi-dependent inhibition of adenylate cyclase and the hydrolysis of phosphoinositides by activation of phospholipase C, which leads to an enhancement of intracellular Ca^{2+} levels able to regulate Ca^{2+}/calmodulin-dependent NOS [19,50].

With respect to CNP, we demonstrated that the activation of the NO-system would be one of the mechanisms involved in CNP vascular and cardiac actions. This peptide would interact with the NPR-C receptor coupled via G proteins leading to the activation of Ca^{2+}-calmodulin dependent NOS in heart and vessels [22]. CNP could also induce vascular relaxation by the activation of NPR-B, PKG, eNOS and sGC [26]. The increase in NO production through these two pathways would induce the accumulation of cGMP, reducing cardiac myocyte contractility and ANP synthesis and secretion in right atria, or inducing vasorelaxation.

Wang et al. showed that BNP increases generation of intracellular cGMP, upregulation of iNOS mRNA expression, iNOS activity and subsequent nitrite generation in growing hypertrophic cardiomyocytes of rat [48]. iNOS or cGMP/PKG pathway inhibition reduced the upregulation of iNOS expression and the increase in iNOS activity induced by BNP, indicating that BNP exerted effects on cardiomyocytes through the induction of iNOS-derived NO by the cGMP pathway.

In summary, these evidences confirm that activation of the NO system would be one of the mechanisms involved in cardiovascular actions of NPs. ANP and CNP activate cardiovascular eNOS without modifications in the expression of the enzyme. Both peptides interact with the NPR-C receptor coupled via Gi proteins leading to activation of Ca^{2+}-calmodulin dependent eNOS in cardiovascular tissues. ANP may also interact with the NPR-A receptor to activate NOS via the PKG-cGMP pathway. The increase in NO production induced by both ANP and CNP increases cGMP, reducing hypertrophy in ventricle and autoregulating ANP synthesis and secretion in right atria and left ventricle and, further, inducing vasorelaxation.

On the other hand, through the NPR-A-cGMP pathway, BNP induces vasodilation partially mediated by NO and prostaglandin release. BNP would exert the antihypertrophic actions in cardiomyocytes by induction of iNOS-derived NO.

Since several cardiovascular disorders are associated with dysfunction of NPs activity, selective modulation of the NPs pathway represents an important therapeutic target. In addition, there are remarkable similarities between the cardiovascular effects of NO and NPs. The cross-talk between these parallel pathways indicates that the activity of both factors is closely linked. The existence of a novel signal transduction mechanism involved in activation of NOS via NPs peptides is currently being explored.

These findings constitute a step in the direction of a better understanding of the complex role that NPs play in the regulation of vascular and cardiac functions due to activation of the NO-system in physiological and perhaps in pathophysiological conditions.

References

[1] T.G. Flynn, Past and current perspectives on the natriuretic peptides, Proc. Soc. Exp. Biol. Med. 213 (1996) 98–104.

[2] T. Maack, Role of atrial natriuretic factor in volume control, Kidney Int. 49 (1996) 1732–1737.

[3] H.H. Chen, J.C. Burnett, C-type natriuretic peptide: the endothelial component of the natriuretic peptide system, J. Cardiovasc. Pharmacol. 32 (1998) 22–28.

[4] L.R. Potter, Domain analysis of human transmembrane guanylyl cyclase receptors Implications for regulation, Front. Biosci. 10 (2005) 1205–1220.

[5] S. Suga, K. Nakao, K. Hosoda, et al., Atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide, Receptor selectivity of natriuretic peptide family, Endocrinology 130 (1992) 229–239.

[6] B.M. Brenner, B.J. Ballermann, M.E. Gunning, et al., Diverse biological actions of atrial natriuretic peptide, Physiol. Rev. 70 (1990) 665–699.

[7] X. Lin, J. Hanze, F. Heese, et al., Gene expression of natriuretic peptide receptors in myocardial cells, Circ. Res. 77 (1995) 750–758.

[8] J. Beltowski, G. Wojcicka, Regulation of renal tubular transport by cardiac natriuretic peptides: two decades of research, Med. Sci. Monit. 8 (2002) 39–52.

[9] R.A. Rose, W.R. Giles, Natriuretic peptide C receptor signalling in the heart and vasculature, J. Physiol. 586 (2008) 353–366.

[10] A. Piech, C. Dessy, X. Havaux, et al., Differential regulation of nitric oxide synthases and their allosteric regulators in heart and vessels of hypertensive rats, Cardiovasc. Res. 57 (2003) 456–467.

[11] P.Y. Cheng, J.J. Chen, M.H. Yen, The expression of heme oxigenase-1 and inducible nitric oxide synthase in aorta during the development of hypertension in spontaneously hypertensive rats, Am. J. Hypertens. 17 (2004) 1127–1134.

[12] G.W. Booz, Putting the brakes on cardiac hypertrophy. Exploiting the NO-cGMP counter-regulatory system, Hypertension 45 (2005) 341–346.

[13] J. Sadowski, B. Badzynska, Intrarenal vasodilator systems: NO, prostaglandins and bradykinin. An integrative approach, J. Physiol. Pharmacol. 59 (2008) 105–119.

[14] L. Kopkan, L. Cervenka, Renal interactions of renin-angiotensin system, nitric oxide and superoxide anion: implications in the pathophysiology of salt-sensitivity and hypertension, Physiol. Res. 58 (2009) S55–S67.

[15] T. Murohara, K. Kugiyama, H. Yasue, Interactions of nitrovasodilators, atrial natriuretic peptide and endothelium-derived nitric oxide, J. Vasc. Res. 33 (1996) 78–85.

[16] S. Cellek, L. Kasakov, S. Moncada, Inhibition of nitrergic relaxations by a selective inhibitor of the soluble guanylate cyclase, Br. J. Pharmacol. 118 (1996) 137–140.

[17] L.G. Melo, A.T. Veress, U. Ackermann, et al., Chronic regulation of arterial blood pressure by ANP: role of endogenous vasoactive endothelial factors, Am. J. Physiol. Heart Regul. Physiol. 275 (1998) H1826–H1833.

[18] C.M. Wei, C.H. Kim, A.A. Khraibi, et al., Atrial natriuretic peptide and C-type natriuretic peptide in spontaneously hypertensive rats and their vasorelaxing actions *in vitro*, Hypertension 23 (1994) 903–907.

[19] M.A. Costa, L.V. Gonzalez Bosc, M. Majowicz, et al., Atrial natriuretic peptide modifies arterial blood pressure through nitric oxide pathway in rats, Hypertension 35 (2000) 1119–1123.

[20] H.G. Nguyen, A. Korach, C. Collura, et al., Differential effects of natriuretic peptides on arterial and venous coronary artery bypass conduits, Ann. Thorac. Surg. 87 (2009) 748–756.

[21] M.A. Costa, R. Elesgaray, C. Caniffi, et al., Role of nitric oxide as a key mediator on cardiovascular actions of atrial natriuretic peptide in spontaneously hypertensive rats, Am. J. Physiol. Heart Circ. Physiol. 298 (2010) H778–H786.

[22] M.A. Costa, R. Elesgaray, C. Caniffi, et al., Role of cardiovascular nitric oxide system on C-type natriuretic peptide effects, Biochem. Biophys. Res. Commun. 359 (2007) 180–186.

[23] A.L. Clavell, A.J. Stingo, C.M. Wei, et al., C-type natriuretic peptide: a selective cardiovascular peptide, Am. J. Physiol. Regul. Integ. Comp. Physiol. 264 (1993) R290–R295.

[24] G. Barletta, C. Lazzeri, S. Vecchiarino, et al., Low-dose C-type natriuretic peptide does not affect cardiac and renal function in humans, Hypertension 33 (1998) 802–808.

[25] F. Brunner, G. Wolkart, Relaxant effect of C-type natriuretic peptide involves endothelium and notoric oxide-cGMP system in rat coronary microvasculature, Cardiovasc. Res. 51 (2001) 577–584.

[26] A. Simon, E.O. Harrington, G.X. Liu, et al., Mechanism of C-type natriuretic peptide -induced endotelial cell hyperpolarization, Am. J. Physiol. Lung Cell. Mol. Physiol. 296 (2009) L248–L256.

[27] C. Caniffi, R. Elesgaray, C. Arranz, et al., C-type natriuretic peptide in espontaneously hypertensive rats: nitric oxide system as a mediator, Peptides 31 (2010) 1309–1318.

[28] K. van der Zandera, A. Houbena, A. Kroona, et al., Nitric oxide and potassium channels are involved in brain natriuretic peptide induced vasodilatation in man, Hypertension 20 (2002) 493–499.

[29] C. Zellner, A.A. Protter, E. Ko, et al., Coronary vasodilator effects of BNP: mechanisms of action in coronary conductance and resistance arteries, Am. J. Physiol. Heart Circ. Physiol. 276 (1999) H1049–H1057.

[30] K.N. Pandey, Biology of natriuretic peptides and their receptors, Peptides 26 (2005) 901–932.

[31] S. Nachshon, O. Zamir, Y. Matsuda, et al., Effects of ANP receptor antagonists on ANP secretion from adult rat cultured atrial myocytes, Am. J. Physiol. Endocrinol. Metab. 268 (1995) E428–E432.

[32] J. Kim, J.H. Han, S.H. Lim, et al., Attenuation of inhibitory effect of CNP on the secretion of ANP from hypertrophied atria, Am. J. Physiol. Regul. Integrative Comp. Physiol. 281 (2001) R1456–R1463.

[33] S.J. Lee, S.Z. Kim, X. Cui, et al., C-type natriuretic peptide inhibits ANP secretion and a trial dynamics in perfused atria: NPR-B-cGMP signaling, Am. J. Physiol. 278 (2000) H208–H221.

[34] H. Leskinen, O. Vuolteenaho, J. Leppaluoto, et al., Role of nitric oxide on cardiac hormone secretion: effect of NG-nitro-L-arginine methyl ester on atrial natriuretic peptide and brain natriuretic peptide release, Endocrinology 136 (1995) 1241–1249.

[35] J.P. Skvorak, J.R. Dietz, Endothelin and nitric oxide interact to regulate stretch-induced ANP secretion, Am. J. Physiol. 273 (1997) R301–R306.

[36] M.A. Costa, R. Elesgaray, A. Loria, et al., Atrial natriuretic peptide influence on nitric oxide system in kidney and heart, Regul. Pept. 118 (2004) 151–157.

[37] M. Hirose, Y. Furukawa, F. Kurogouchi, et al., C-type natriuretic peptide increases myocardial contractility and sinus rate mediated by guanylyl cyclase-linked natriuretic peptide receptors in isolated, blood-perfused dog heart preparations, Pharmacol. Exp. Ther. 286 (1998) 70–76.

[38] A. Nir, D.F. Zhang, R. Fixler, et al., C-type natriuretic peptide has a negative inotropic effect on cardiac myocites, European J. Pharmacol. 412 (2001) 195–201.

[39] J.M. Hare, J.S. Stamler, NOS: modulator, not mediator of cardiac performance, Nat. Med. 5 (1999) 273–274.

[40] R. Gyurko, P. Kuhlencordt, M.C. Fishman MC, et al., Modulation of mouse cardiac function *in vivo* by eNOS and ANP, Am. J. Physiol. Heart Circ. Physiol. 278 (2000) H971–H981.

[41] P.A. Ortiz, J.L. Garvin, Cardiovascular and renal control in NOS-deficient mouse models, Am. J. Physiol. Regul. Integr. Comp. Physiol. 284 (2003) 628–638.

[42] M. Pierkes, S. Gambaryan, P. Boknik, et al., Increased effects of C-type natriuretic peptide on cardiac ventricular contractility and relaxation in guanylyl cyclase A-deficient mice, Cardiovasc. Res. 53 (2002) 852–861.

[43] A.J.B. Brady, J.B. Warren, P.A. Poole-Wilson, et al., Nitric oxide attenuates cardiac myocyte contraction, Am. J. Physiol. 265 (1993) H176–H182.

[44] T. Tokudome, T. Horio, T. Soeki, et al., Inhibitory effect of C-type natriuretic peptide (CNP) on cultured cardiac myocyte hypertrophy: interference between CNP and endothelin-1signaling pathways, Endocrinology 145 (2004) 2131–2140.

[45] A. Calderone, C.M. Thaik, N. Takahashi, Nitric oxide, atrial natriuretic peptide and cyclic GMP inhibit the growth promoting effects of norepinephrine in cardiac myocytes and fibroblasts, J. Clin. Invest. 101 (1998) 812–818.

[46] M. Kuhn, R. Roltwick, H.A. Baba, et al., Progressive cardiac hypertrophy and dysfunction in atrial natriuretic peptide (GC-A) deficient mice, Heart 87 (2002) 368–374.

[47] M.J. Lopez, S.K. Wong, I. Kishimoto, et al., Salt-resistant hypertension in mice lacking the guanylyl cyclase-A receptor for atrial natriuretic peptide, Nature 378 (1995) 65–68.

[48] T. Wang, M. Yan, J. Li, et al., The role of iNOS-derived NO in the antihypertrophic actions of B-type natriuretic peptide in neonatal rat cardiomyocytes, Mol. Cell. Biochem. 302 (2007) 169–177.

[49] B. Ren, Y. Shen, H. Shao, et al., Brain natriuretic peptide limits myocardial infarct size dependent of nitric oxide synthase in rats, Clin. Chim. Acta 377 (2007) 83–87.

[50] R. Elesgaray, C. Caniffi, D. Rodríguez Ierace, et al., Signaling cascade that mediates endothelial nitric oxide synthase activation induced by atrial natriuretic peptide, Regul. Pept. 151 (2008) 130–134.

[51] M.A. Costa, R. Elesgaray, A.M. Balaszczuk, et al., Role of NPR-C natriuretic receptor in nitric oxide system activation induced by atrial natriuretic peptide, Regul. Pept. 135 (2006) 63–68.

[52] J.S. McLay, P.K. Chatterjee, A.G. Jardine, et al., Atrial natriuretic factor modulates nitric oxide production: an ANF-C receptor-mediated effect, J. Hypertens. 13 (1995) 625–630.

[53] K.S. Murthy, B. Teng, B. Jin, et al., G protein-dependent activation of smooth muscle eNOS via natriuretic peptide clearance receptor, Am. J. Physiol. 275 (1998) C1409–C1416.

[54] M. Kuhn, Molecular physiology of natriuretic peptide signaling, Basic Res. Cardiol. 99 (2004) 76–82.