Interactions between the sympathetic nervous system and the cardiac natriuretic peptide system

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Received 1 January 2004; received in revised form 20 April 2004; accepted 6 May 2004
Time for primary review 23 days

Abstract

The sympathetic nervous system (SNS) and the cardiac natriuretic peptide system (NPS) are fundamentally important neurohumoral systems for cardiovascular regulation. Their mutual interactions have been subject to numerous experimental and human studies. In the current manuscript, results from in vivo and in vitro studies will be reviewed with a focus on sympathetic outflow on the control of natriuretic peptide release.

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Keywords: Sympathetic nervous system; Alpha receptor; Beta-receptor; Heart failure; ANP; Natriuretic peptides; Interactions; Cross-talk

1. Introduction

The sympathetic nervous system (SNS) and the cardiac natriuretic peptide system (NPS) are fundamentally important for cardiovascular regulation. Forty years ago, release of norepinephrine (NE) from cardiac nerve fibres has first started the perception of the heart as an endocrine organ [1]. Twenty years ago, this observation was followed by studies which have shown natriuretic effects of atrial myocardial tissue extracts and have led to the discovery of atrial natriuretic peptide [2,3] (ANP). Since then, the interactions between both systems have been subject to numerous experimental and human studies.

Most work has been done in cultured cardiomyocytes, where phenylephrine (PHE) leads to synthesis and release of the natriuretic peptides as well as cellular hypertrophy. To date, phenylephrine-induced activation of ANP is probably the most widely used surrogate parameter for myocyte hypertrophy in this experimental setting and has facilitated important discoveries which relate to the induction of myocyte growth [4–7]. Studies in intact animals have confirmed that cardiac sympathetic stimulation facilitates release of ANP and BNP and have further demonstrated that the clearance of the natriuretic peptides in extracardiac tissue is also regulated by sympatho-adrenergic stimuli. They have further allowed insight into the effects of the natriuretic peptides on arterial baroreflex and demonstrated their sympatho-inhibitory actions. Lastly, these studies helped to identify activation of the natriuretic peptides as one potential mechanism that facilitates the action of beta-adrenergic receptor blockers.

2. Cell culture studies

In vitro, several patterns of interaction between the sympathetic nervous and the natriuretic peptide system have been detected. These interactions are described in the following paragraphs, graphically depicted in Fig. 1 and listed in Table 1.

2.1. Role of adrenergic receptors for natriuretic peptide stimulation (Fig. 1)

A stimulatory effect of the alpha-adrenergic receptor on ANP secretion has already been described in 1988 [8,9],
only 4 years after the purification and sequence determination of ANP [3]. Matsubara et al. [9] studied primary cultures of atrial myocytes from neonatal rats. In these cells, phenylephrine stimulated ANP secretion and this effect could be blocked by the alpha-adrenergic receptor antagonist prazosin. In addition, an activator of protein kinase C (PKC) induced a dose-dependent increase in ANP secretion which was also calcium-dependent. Similar observations were made in adult rat atrial myocytes where stimulation of the alpha-1 receptor stimulated ANP release [8]. In contrast, isoproterenol, which predominantly stimulates the beta-adrenergic receptor, had no effect on ANP release. The respective roles of the alpha- and beta-adrenergic receptors and the protein kinases A and C were further investigated by Shields and Glembotski [10] who found that ANP secretion from neonatal rat atrial myocytes is enhanced by phenylephrine and other activators of protein kinase C and decreased by isoproterenol and other activators of protein kinase A both under basal and stimulated conditions. The authors concluded that ANP secretion is enhanced through activation of the alpha-adrenergic receptors and attenuated through activation of the beta-adrenergic receptors, respectively [10].

First indirect evidence that the induction of ANP by alpha 1-adrenergic agonists is mediated via the alpha 1a receptor stems from work by Knowlton et al. [11], who could demonstrate that an alpha 1b-selective antagonist had no effect on the adrenergically mediated induction of ANP or the associated increase in myocardial cell size. This concept has later been confirmed by studies employing a selective alpha 1a agonist which led to a significant elevation of ANP messenger RNA and secretion and was totally abolished by a selective alpha 1a antagonist. Furthermore, alpha 1a stimulation resulted in a further increase in alpha 1a receptor mRNA and a decrease in alpha 1b mRNA, suggesting a positive feedback between alpha 1a stimulation and receptor expression and a negative feedback with alpha 1b receptor expression [12].

The signal transduction of adrenergic receptor-stimulated ANP secretion has been assessed in cultured myocytes from adult and neonatal rats as well as in intact adult atrial muscle. While the effects associated with stimulation of the alpha-adrenergic receptors are very similar, the effects associated with stimulation of the beta-adrenergic receptors differ in contracting myocytes. Specifically, beta-adrenergic stimulation and elevation of intracellular cAMP inhibits basal and alpha-1-stimulated ANP secretion in neonatal rat atrial myocytes [10], non-contracting intact atria [13] and perfused beating rabbit atria [14], while it increases ANP secretion in electrically paced intact atria [15]. As a potential explanation, it has been speculated that since atrial myocytes are not as greatly stretched in the culture system because of their attachment to the non-deformable substratum in comparison to atrial myocytes in situ, a direct inhibitory action of cAMP signalling on ANP secretion may predominate in culture while ANP secretion might be indirectly increased in intact atria because of the positive inotropic and chronotropic effects of cAMP in situ [16]. The effects of adrenergic stimulation on ANP secretion in different culture settings are depicted in Table 2.

Regarding the effects of alpha-adrenergic signalling on the second cardiac natriuretic peptide, BNP, there is a qualitative similarity with ANP, but a quantitative difference regarding the time course of activation as well as mRNA stability. Hanford et al. [17,18] have demonstrated that while ANP and BNP are activated by alpha 1-adrenergic stimulation to a similar extent, strong increases of BNP mRNA were already observed 1 h after exposure while similar increases in ANP mRNA were evident only after 6–8 h. Moreover, while ANP mRNA levels continued to increase to 24 h, maximal levels of BNP mRNA were observed already 4 h after treatment. Furthermore, induction of BNP appeared to be the result of mRNA stabilisation and the short-lived BNP transcripts were stabilised by alpha 1-adrenergic stimulation while the half-life of the long-lived ANP transcripts did not change. The more rapid induction of BNP was also reported by Nakagawa et al. [19], who could further demonstrate that phenylephrine-stimulated BNP expression occurs as rapidly as the “immediate/early” gene c-fos. Consequently, Nakagawa first

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**Table 1**

Local and systemic interactions between the sympathetic nervous and the natriuretic peptide system

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Stimulus</th>
<th>Receptor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyocyte</td>
<td>PHE</td>
<td>Alpha1a-AR</td>
<td>ANP ↑, BNP ↑</td>
</tr>
<tr>
<td>Cardiomyocyte</td>
<td>ISO</td>
<td>Beta1-AR</td>
<td>ANP ↓, BNP ↓</td>
</tr>
<tr>
<td>Cardiomyocyte</td>
<td>ANP/BNP</td>
<td>NPR-A</td>
<td>ANP ↓, BNP ↓</td>
</tr>
<tr>
<td>VSMC</td>
<td>ISO</td>
<td>Beta2-AR</td>
<td>NPR-C ↓, NPR-A +/-</td>
</tr>
</tbody>
</table>

PHE denotes phenylephrine; AR, adrenergic receptor; ISO, isoproterenol; NPR-A, natriuretic peptide receptor A; NPR-C, natriuretic peptide receptor C.
suggested BNP as an “emergency” cardiac hormone against ventricular overload.

For the induction of ANP synthesis and excretion, alpha-adrenergic signalling requires calcium as a co-factor. Decreasing calcium concentration from a physiological level to very low levels partially diminishes the stimulatory effects of phenylephrine on ANP secretion [20]. Furthermore, addition of a calcium channel antagonist results in a rapid decline of ANP expression whereas a calcium channel agonist increases ANP expression. Both the effects of phenylephrine and the calcium channel agonist can be completely blocked by a calcium/calmodulin inhibitor. The authors concluded that alpha-adrenergic stimulation of ANP gene expression involves the sustained activation of calmodulin-regulated kinases as well as activation of protein kinase C [21]. The role of calcium was also assessed by Schiebinger et al. [22], who could demonstrate that in superfused beating atria, calcium influx is necessary to initiate alpha-1 agonist-stimulated ANP secretion. Whereas calcium entry through L-type calcium channels is responsible for a considerable portion of this effect, calcium release from the sarcoplasmatic reticulum does not play a role. Furthermore, while calcium influx is necessary to initiate alpha 1 agonist-stimulated ANP secretion, maintenance of this effect is not dependent of calcium influx [22].

Alpha-adrenergic stimulation of ANP and BNP is now well established in the experimental setting. It occurs downstream of early and critical events in the signalling cascade of myocyte hypertrophy and ANP is probably the most widely utilized biochemical surrogate parameter for cellular hypertrophy in this experimental setting. Such, it has been shown that phenylephrine-induced stimulation of ANP and BNP occurs downstream of chronic activation of extracellular-signal-regulated protein kinases (ERKs). ERK belongs to the three mitogen-activated protein kinase (MAPK) subfamilies which also consists of c-Jun N-terminal kinases (JNKs) and p38-MAPK. The development of phenylephrine-induced increases of ANP as well as myocyte size and protein synthesis can be prevented by ERK inhibition [6,23] or by inhibition of the upstream activator of ERK, mitogen-activated protein kinase (MAPK)/ERK kinase (MEK) [24]. Phenylephrine-induced stimulation of ANP and BNP also occurs downstream of the E2F transcription factors, a family of cell cycle progression transcription factors which are otherwise crucial for normal cardiac development [25]. In vitro, it has been shown that the development of phenylephrine-induced increases of ANP and BNP as well as myocyte hypertrophy and protein synthesis can be prevented by inhibition of these transcription factors.

2.2. Autocrine role of the NPR-A receptor (Fig. 1)

Activation of myocardial ANP depends not only on adrenergic stimulation but also on activation of its own biological receptor, the NPR-A receptor. The discovery of HS-142-1, an unspecific natriuretic peptide receptor antagonist, has provided the unique opportunity to assess potential autocrine effects of ANP on the myocyte. When endogenous ANP was blocked by HS-142-1, basal as well as phenylephrine-stimulated protein synthesis, gene expression of skeletal alpha actin, beta-myosin heavy chain, and ANP as well as myocyte size were increased in a concentration-dependent manner [26]. This observation suggests that endogenous ANP, through receptor-dependent feedback, inhibits myocyte hypertrophy under basal conditions as well as under adrenergic stimulation.

2.3. Role of adrenergic receptors for natriuretic peptide clearance (Table 2)

Another interesting interaction between the sympathetic nervous system and the natriuretic peptides has been demonstrated for extracardiac tissue. In cultured vascular smooth muscle cells, Kishimoto et al. [27] have demonstrated that the natriuretic peptide clearance receptor (NPR-C) is transcriptionally down-regulated and ANP clearance is attenuated secondary to beta 2-adrenergic stimulation through isoproterenol. The catecholamine-induced down-regulation of the clearance receptor was antagonized by a beta 2-selective adrenergic antagonist but not by alpha 1 or beta 1-adrenergic antagonists. By contrast, neither the NPR-A nor the NPR-B receptor concentration was affected. This finding strongly suggests that activation of the sympathetic nervous system increases the natriuretic peptides by attenuating their extracardiac clearance in the vascular wall. As discussed later, this effect also appears to be part of the therapeutic spectrum of beta-receptor blockers.

3. In vivo studies

The interactions between the sympathetic nervous system and the natriuretic peptides have been assessed in several in
vivo studies. These studies provided the opportunity to assess the importance of the alpha- and beta-adrenergic receptors for ANP and BNP release and clearance as well as the importance of the natriuretic peptides for sympathetic outflow and baroreflex control. These experiments have been carried out in the intact laboratory animal but also in human beings.

3.1. Role of adrenergic receptors for natriuretic peptide stimulation

In the intact animal, phenylephrine increased plasma ANP without altering atrial pressures when directly infused into the coronary arteries of anesthetized pigs [28]. In contrast, beta-adrenergic stimulation by isoproterenol reduced plasma ANP by 20% despite a rise in left atrial pressure which by itself would have increased a plasma ANP by 53%. Therefore, the authors concluded that alpha-adrenergic stimulation increases and beta-adrenergic stimulation inhibits natriuretic peptide release by a direct action. However, the direct effects are relatively small as compared with the effects of a moderate increase in atrial filling pressure. A very similar observation has also been made earlier in the isolated perfused heart by Currie and Newman [29], who found that the release of ANP in the coronary effluent from isolated rat hearts is stimulated by the administration of norepinephrine in a dose-dependent manner and inhibited by concomitant alpha-blockade. In contrast, infusion of isoproterenol failed to stimulate ANP release.

3.2. Importance of the natriuretic peptides for the baroreflex and sympathetic nervous outflow

3.2.1. Animal studies

The effects of ANP on baroreflex control have been assessed in chronically instrumented conscious rats. Reflex sensitivity was calculated as slope of the linear relationship between pulse interval and mean arterial pressure in the presence and absence of ANP. Here, ANP enhanced the bradycardic response to phenylephrine but reduced the tachycardic response to nitroprusside, so that the authors concluded that ANP modulates the arterial baroreflex in a complex fashion [30]. The baroreceptor reflex was also studied by central microinjection of ANP into the caudal nucleus tractus solitarii. Here, the heart rate and arterial pressure response during phenylephrine infusion was blunted in the salt-sensitive SHR rat but not in the WKY rats. In contrast, microinjection of a monoclonal ANP antibody enhanced the sensitivity of baroreceptor reflex control in the SHR rat [31,32]. This observation was confirmed in conjunction with measurement of lumbar sympathetic nervous activity in SHR but not WKY rats, so that the authors concluded that endogenous ANP in the caudal nucleus tractus solitarii might contribute to the development and/or maintenance of hypertension (in SHR rats) by blunting baroreflex-mediated control of sympathetic nervous system activity [32].

The contribution of central adrenergic receptors has also been studied with respect to the involvement in volume expansion-induced release of ANP [33]. When the alpha-receptor blocker phentolamine was injected into the anterior ventral third ventricular region of the hypothalamus prior to volume expansion, the ANP response was markedly suppressed. The authors therefore concluded that activation of an alpha-adrenergic synapse is part of the stimulatory reflex through which distension of baroreceptors within the atria leads to cardiac ANP release and also involves neurons which stimulate central ANP neurons via muscarinic receptors.

There is also evidence of ANP in the cardiac conduction system as well as in ganglia which are involved in the neuronal regulation of the heart. Here, ANP also appears to affect the cardiac autonomic nervous system by sympathoinhibitory and vagoexcitatory actions (see Refs. [34,35] for an overview).

3.2.2. Human studies

The effects of exogenous natriuretic peptides on the autonomous nervous system have been mostly assessed in healthy individuals. Initially, activation of the sympathetic nervous system with increases of plasma norepinephrine and peripheral resistance [36] as well as muscle sympathetic efferent activity [37] was described during steady state infusion of ANP. However, these observations appear to predominantly result from reflex activation secondary to decreased central venous pressure during ANP infusion and sympathetic activity was unchanged when central venous pressure was kept constant through head-down tilt or lower body positive pressure [37]. Furthermore, during alternating neck suction and pressure, the infusion of exogenous ANP significantly blunted reflex tachycardic responses while reflex bradycardic responses were unaltered. The authors speculated that these responses may be due to a sensitization of cardiac receptors and augmentation of cardiac–vagal afferent traffic by ANF, which diminishes reflex cardiac–sympathetic outflow during carotid baroreceptor unloading [38]. The effects of exogenous ANP on the sympathetic and parasympathetic nervous system in healthy individuals were also assessed by means of spectral analysis of heart rate variability. Here, the authors concluded that ANP lowered parameters of sympathetic nervous activity but had no significant effects on indicators of parasympathetic nervous activity which is consistent with a relative sympatho-inhibitory action of ANP [39].

The effects of BNP on cardiac and whole body sympathetic nervous activity have been assessed in healthy human subjects as well as in patients with congestive heart failure [40]. The authors could show that low-dose BNP, in the absence of blood pressure effects, reduced cardiac norepinephrine spillover in control subjects and CHF patients but
not whole body spillover. Renal norepinephrine spillover remained unchanged in control subjects but was reduced in patients with CHF secondary to low-dose BNP. The authors therefore concluded that physiologic BNP concentrations have a sympato-inhibitory effect with a predominance of cardiac sympathetic inhibition and inhibition of renal sympathetic nerve activity in heart failure patients. Infusion of pharmacological doses of BNP in patients with decompensated heart failure resulted in cardiac unloading, reduction of systemic vascular resistance and improved cardiac output without reflex increase in heart rate as well as a decrease in plasma norepinephrine and without deleterious effects on renal hemodynamics [41]. These results indirectly also point to a sympato-inhibitory effect of BNP.

The infusion of exogenous natriuretic peptides has meanwhile gained therapeutic importance and ANP (in Japan) and BNP (in the USA) are now administrated to patients with decompensated congestive heart failure. While most of the pharmacological effects appear to result from their direct hemodynamic and renal actions, sympato-inhibition of ANP and BNP through neurohumoral cross-talk may also be part of their beneficial therapeutic effects.

3.3. Effect of beta-receptor blockade on natriuretic peptides

Beta-receptor blockade is a pharmacological intervention with paramount importance in the treatment of cardiovascular diseases. While the therapeutic effects of beta-receptor blockade are thought to primarily result from attenuation of the inotropic and chronotropic effects of the cardiac beta-adrenergic receptor, evidence from animal and human studies has suggested that extracardiac activation of the natriuretic peptides is also an important component.

In patients with hypertension who were chronically treated with the beta-blocker propranolol [42] or atenolol [43], increases in plasma ANP of approximately 40% were observed. The authors concluded that beta-adrenergic receptor blockade elevates plasma ANP and that increased ANP may play a role in the compensatory mechanism in response to beta-adrenergic receptor blockade. The observation that circulating natriuretic peptides are elevated by chronic beta-adrenergic receptor blockade has also been confirmed in population-based studies. In a substudy to the MONICA Augsburg study, we found that 80 of 672 subjects who used beta-receptor antagonists were characterized by substantially elevated ANP and BNP plasma concentrations [44]. This effect was present even in the absence of hypertension and left ventricular dysfunction and particularly pronounced in left ventricular hypertrophy (Fig. 2) and could not be demonstrated for other antihypertensive agents. The additional stimulation of the second messenger cGMP further suggests a functional activation of the cardiac natriuretic peptide system and a contribution of the natriuretic peptides to the therapeutic mechanisms of beta-receptor antagonists. A very similar observation was also reported for the MONICA Glasgow study [45]. Here, the 108 subjects who were receiving a beta-receptor blocker among a total of 1396 subjects were characterized by statistically significantly increased BNP concentrations. Furthermore, in contrast to other antihypertensive agents, only beta-blocker treatment independently predicted increased BNP concentrations after adjustment for age, ejection fraction, gender, hypertension and ischemic heart disease.

The underlying mechanism might include a decreased clearance of ANP and BNP as has been suggested by animal studies. Indeed, treatment of stroke-prone spontaneously hypertensive rats with the beta-receptor antagonist propranolol decreased receptor densities and mRNA levels of the natriuretic peptide clearance receptor (NPR-C) in aortic and pulmonary tissue while cardiac expression of ANP as well as aortic and renal expression of the natriuretic peptide A-receptor remained unchanged [46]. A very similar observation was made when stroke-prone spontaneously hypertensive rats were chronically treated with carvedilol [47]. Together with a significant increase in plasma ANP concen-
trations, the mRNA of the NPR-C receptor was significantly decreased in tissue from aorta and lung and the biological half-life of exogenous ANP in circulating blood was prolonged. In addition, basal and ANP-stimulated cGMP content in the aorta was significantly enhanced. Together, these results suggest that down-regulation of the NPR-C may account for a sizeable portion of the hypotensive actions and enhanced vascular response of beta-receptor blockers.

Taken together, beta-receptor blockade might act through three different mechanisms to augment the cardiac natriuretic peptides:

(I) Withdrawal of suppressive effects through myocardial beta-adrenergic receptor blockade.
(II) Re-direction of sympathetic stimuli from beta- to alpha-adrenergic receptors with subsequent stimulation of cardiac ANP and BNP synthesis, secretion and mRNA stability.
(III) Decreased extracardiac clearance of ANP and BNP through down-regulation of the NPR-C receptor in lung, kidney and the vascular wall.

This finding might be of particular importance when BNP is serially assessed as a heart failure marker in patients with congestive heart failure who are started on beta-blockers. In this respect, an interesting observation has been made with congestive heart failure who are started on beta-blockers. Here, BNP concentrations generally decreased over time in the valsartan-treated group and slightly increased in the placebo-treated groups. Most interestingly, however, BNP markedly increased in placebo-treated patients who received beta-blockade but no concomitant ACE inhibition. This observation suggests that BNP testing might be misleading in CHF patients treated with beta-blockers. Here, increased BNP might be due to the abovementioned neurohumoral interactions rather than a deterioration of cardiac functional status. Since this effect was not observed in patients with concomitant treatment by ACE inhibitors or angiotensin receptor blockers, it will, however, only be relevant for a minority of heart failure patients.

4. Summary

The interplay between the sympathetic nervous system and the cardiac natriuretic peptide system is crucially important for the regulation of cardiovascular function. The alpha receptor-mediated arm of the sympathetic nervous system activates synthesis and secretion of the cardiac natriuretic peptides through enhanced gene expression and stabilisation of messenger RNA (BNP). The natriuretic peptides affect sympathetic nervous outflow and baroreceptor reflex. Pharmacological interventions markedly affect the balance between activation of the sympathetic nervous and the natriuretic peptide system. ANP and BNP administration decrease sympathetic outflow and the steepness of the baroreceptor reflex while withdrawal of beta-adrenergic receptor activity augments the natriuretic peptide system.

References


