Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones

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Thirty years ago, De Bold et al. (20) reported that atrial extracts contain some biological active peptides, which promote a rapid and massive diuresis and natriuresis when injected in rats. Several endogenous peptide hormones with natriuretic and vasodilator activity have been identified in the human blood and peripheral tissues (3, 30, 69, 85, 86). Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and their related peptides are predominantly produced by atrial and ventricular cardiomyocytes. The term “cardiac natriuretic hormones” (CNHs) will be used in this review to indicate these two families of natriuretic peptides. Another natriuretic peptide, named C-type natriuretic peptide (CNP), is predominantly produced by the endothelial cells, including those of cardiac vessels. Finally, urodilatin is an NH2-terminal (NT) 4-amino acid (aa) extended form of ANP, which is produced by the same ANP gene and secreted into the urine by renal tubular cells (16, 34, 69).

From the original observations made 30 years ago, the advances in this particular research field have determined a complete revision about the role of the heart. It is now clear that the heart also exerts an endocrine function and in this way plays a key role in the regulation of cardiovascular and renal systems. The aim of this review is to discuss some recent insights and still-debated findings regarding the cardiac natriuretic hormones (CNHs) produced and secreted by cardiomyocytes (i.e., atrial natriuretic peptide and B-type natriuretic peptide). The functional status of the CNH system depends not only on the production/secretion of CNHs by cardiomyocytes but also on both the peripheral activation of circulating inactive precursor of natriuretic hormones and the transduction of the hormone signal by specific receptors. In this review, we will discuss the data supporting the hypothesis that the production and secretion of CNHs is the result of a complex integration among mechanical, chemical, hemodynamic, humoral, ischemic, and inflammatory inputs. The cross talk among endocrine function, adipose tissue, and sex steroid hormones will be discussed more in detail, considering the clinically relevant relationships linking together cardiovascular risk, sex, and body fat development and distribution. Finally, we will review the pathophysiological role and the clinical relevance of both peripheral maturation of the precursor of B-type natriuretic peptides and hormone signal transduction.

B-type natriuretic peptide; sex steroids; adipokines; heart failure; cardiovascular risk

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CNHs are synthesized by cardiomyocytes as prohormones (i.e., proANP and proBNP), which are then split into two fragments at the time of secretion: the longer fragment includes the inactive NT peptide (i.e., NT-proANP and NT-proBNP), whereas the shorter one (i.e., COOH-terminus fragment) represents the active hormone (i.e., ANP and BNP) (34). Studies on structure-activity relationships have underscored the importance of the ring structure of CNHs, related to a disulfide cysteine bridge, which is necessary for the binding to the specific receptors. For this reason, only ANP and BNP, presenting the disulfide bridge in the peptide chain, hold hormonal activity.

Atrial cardiomyocytes store prohormones (proANP and proBNP) in secretory granules (16, 34, 69). In particular, human BNP is synthesized as a 134-aa precursor protein (preproBNP) and is subsequently processed during secretion to form the 108-aa peptide, proBNP. The propeptide hormones of cardiac natriuretic peptides can be enzymatically cleaved by proprotein convertases produced in the cardiomyocytes, such as corin and furin (24, 34, 43, 49). Indeed, the precursor proBNP is processed to form the 76-aa NT peptide (i.e., NT-proBNP), and then the biologically active 32-aa COOH-terminal peptide (i.e., BNP).

Although the distension of atrial and ventricular cardiomyocytes is generally considered the main mechanical stimulus for the production/secretion of ANP and BNP (57), endothelin-1, α-adrenergic agonists, and angiotensin II are also powerful stimulators of production/secretion of CNHs by cardiomyocytes (34, 52, 67) (Fig. 1 and Table 1). Furthermore, myocardial ischaemic and perhaps hypoxia per se can induce the synthesis/secretion of BNP and its related peptides by ventricular cells, even when isolated and cultured (8, 12, 33, 89, 94) (Fig. 1). Mammalian cells respond to low oxygen with an increased expression of several hypoxia-inducible genes. The master regulator of this cellular adaptation to hypoxia is the hypoxia-inducible factor (HIF)-1 (Refs. 8, 13, 104).

According to these findings, under physiological conditions, ventricular myocardium produces only a limited amount of BNP; conversely, several pathophysiological mechanisms, such as ventricular hypertrophy, inflammation, and fibrosis, stimulate BNP production and release from ventricular cardiomyocytes (19, 60, 69, 77, 102). Furthermore, myocardial ischaemia and hypoxia per se can induce the synthesis/secretion of BNP and its related peptides by ventricular cells, even when isolated and cultured (8, 12, 33, 89, 94) (Fig. 1).

Mammalian cells respond to low oxygen with an increased expression of several hypoxia-inducible genes. The master regulator of this cellular adaptation to hypoxia is the hypoxia-inducible factor, which is a heterodimeric transcription factor. Some studies indicate that low oxygen conditions induce the expression of hypoxia-inducible factor-1α, which in turn acti-

![Fig. 1. Highly schematic representation of brain natriuretic peptide (BNP) gene regulation in the cardiomyocyte. BNP production by cardiomyocytes may be affected by a huge number of neurohormones, cytokines, and survival and growth factors, as well as by mechanical strain and hypoxia. The stimulation (or inhibition) of the MAPK activity and the transcription factor NF-κB may play a relevant role in many of these regulatory pathways (according to Refs. 8, 13, 19, 34, 57, 60, 67, 91, 93, and 104). As indicated, low oxygen conditions (hypoxia) can activate both atrial natriuretic peptide and BNP transcription throughout an alternative pathway by inducing the expression of hypoxia-inducible factor (HIF)-1α (Refs. 13, 104). GPCR, G protein-coupled receptor; PKC, protein kinase C; PI3K, phosphoinositide 3-kinase; RTK, receptor of tyrosine kinase; ACE, angiotensin-converting enzyme; ET, endothelin.](http://ajpheart.physiology.org/)
vates both ANP and BNP transcription (13, 104). These data may explain the increased BNP levels observed in patients with ischemic heart diseases and preserved ventricular function (16, 35, 69).

Studies using culture of cardiomyocytes (especially from rodents) have demonstrated that several factors (including calcium, catecholamines, endothelins, angiotensin II, and some cytokines) can regulate the expression of ANP and BNP genes throughout the same transcriptional factors, including p38 mitogen-activated protein kinase (MAPK) (19, 34, 41, 50, 52, 56, 60, 91), as indicated in Fig. 1. A still unresolved question is the role of insulin on the regulation of production/secretion of CNHs by cardiomyocytes. Some studies (2, 6, 18) indicated that insulin has a potent acute anti-inflammatory effect, which is mediated by the inhibition of transcription factor NF-κB. According to these studies (2, 6, 18), an inhibitory role of insulin on the production/secretion of CNHs may be hypothesized. However, to our knowledge, only the study by Tukudome et al. (92) was performed with the specific aim to examine the direct effects of insulin on the secretion/production of CNHs from cardiomyocytes. This study reported that insulin increased ANP secretion and gene expression in cultures of rat cardiomyocytes, whereas glucose had no effect (92). These conflicting results suggest that further studies are necessary to clarify the complex biochemical pathways and molecular mechanisms responsible for CNH production in cardiomyocytes (34).

The Cross Talk Between the Cardiac Endocrine Function and Adipose Tissue System

Since some adipokines (such as leptin, resistin, and visfatin) are able to activate the transcription factor NF-κB (1, 55, 84, 93, 101), it may be hypothesized that these adipokines also have a stimulatory action on ANP and BNP throughout this metabolic pathway. However, Mascarenos et al. (64) reported that leptin has antihypertrophic action in vivo in mice, rather than a hyperthrophic effect, as expected by the studies in the culture of ventricular cardiomyocytes. This effect is indeed mediated in vivo by CNHs, since leptin was found to increase the expression of the ANP gene by the activation of nuclear factor of activated T-cell domain of ANP gene promoter (64). On the contrary, Yuan et al. (107) reported that intravenous infusion of leptin reduces ANP plasma levels via an NO-dependent mechanism in rats. Therefore, these studies point out that CNH production/secretion by cardiomyocytes can be differently regulated by the same biological factor (such as leptin) throughout multiple metabolic pathways activated, or inhibited, according to different pathophysiological conditions.

On the other hand, recent findings indicated that CNHs have a role in the regulation of fat tissue function and growth (17) and also exert potent lipolytic effects in human fat cells (52). Furthermore, ANP can increase the production of adiponectin (95), a polypeptide involved in glucose and free fatty acid metabolism (so to be protective in diabetes and metabolic syndrome), whereas the release of leptin is inhibited in culture of human adipocytes (28, 68).

The above-mentioned studies indicate that there is a crosstalk between the cardiac endocrine function and adipose tissue. From a pathophysiological point of view, further studies on the interrelationship between CNHs and adipokines may allow new insights on the link between metabolic disorders (such as diabetes mellitus, metabolic syndrome, and obesity), body fat distribution, and increased cardiovascular risk (7, 15). Indeed, a still unexplained finding is the lower CNH levels found in obese compared with lean health subjects and patients with heart failure (HF) (15). Although the increased expression of clearance natriuretic peptide receptor (i.e., NPR-C) in fat tissue can, at least in part, explain this finding (see Resistance to the Biological Effects of CNHs), the increased production of some adipokines may be a good explanation for a link relating the increased visceral fat tissue to reduced circulating levels of CNHs. A good candidate should be a biological substance (or more substances) showing inhibitory properties on the production/secretion of CNHs and released by fat tissue.

Table 1. Biological factors suggested to stimulate or inhibit the production/secretion of CNHs in vivo or in cell culture of cardiomyocytes

<table>
<thead>
<tr>
<th>Suggested Factors</th>
<th>Suggested Mean Intracellular Signaling Mechanism</th>
<th>References</th>
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<tbody>
<tr>
<td>Stimulating</td>
<td></td>
<td></td>
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<tr>
<td>Mechanical strain</td>
<td>Transcription factor NF-κB activated by p38 MAPK</td>
<td>57</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Transcription factor NF-κB activated by p38 MAPK</td>
<td>34, 52, 67</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Transcription factor NF-κB activated by p38 MAPK</td>
<td>34, 52, 67</td>
</tr>
<tr>
<td>α-Adrenergic agents</td>
<td>Transcription factor NF-κB activated by p38 MAPK</td>
<td>16, 34, 52, 67</td>
</tr>
<tr>
<td>Arginine vasopressin</td>
<td>Ca²⁺ influx and PKC</td>
<td>97</td>
</tr>
<tr>
<td>Cytokines (including IL-1, IL-6, TNF-α)</td>
<td>Transcription factor NF-κB activated by p38 MAPK</td>
<td>19, 60</td>
</tr>
<tr>
<td>Growth factors (such as bFGF)</td>
<td>MAPK</td>
<td>27, 39</td>
</tr>
<tr>
<td>Prostaglandins (such as PGI₂, and PGD₂)</td>
<td>PLC, IP₃, PKC, and MLCK pathway</td>
<td>5, 54</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>Transcription factor NF-κB activated by p38 MAPK</td>
<td>19</td>
</tr>
<tr>
<td>Chromogranin B</td>
<td>Transcription factor NF-κB and IP₃/Ca²⁺ influx</td>
<td>41</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Thyroid hormone regulatory element</td>
<td>4, 21, 32, 65, 66, 69</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Glucocorticoid responsive element</td>
<td>21, 65, 66, 69</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Not yet determined</td>
<td>51, 61</td>
</tr>
<tr>
<td>Inhibiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgens</td>
<td>Not yet determined</td>
<td>9, 42, 76</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Transcription factor JMJ</td>
<td>37, 48, 107</td>
</tr>
</tbody>
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CNH, cardiac natriuretic hormone; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; IL, interleukin; TNF, tumor necrosis factor; bFGF, basic fibroblastic growth factor; PG, prostaglandin; PLC, phospholipase C; IP₃, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; JMJ, jumonji domain-containing protein.
The Cross Talk Between Cardiac Natriuretic and Sex Steroid Hormones

According to the hypothesis that CNHs share complex interactions with the neurohormonal system, the interest on the interrelationships between cardiac endocrine and gonadal functions progressively increased throughout the first 10 years of this century. Cardiovascular risk is significantly lower in healthy premenopausal women compared with men, a difference abolished after menopause, suggesting an important role for female sex steroid estrogens on pathophysiological mechanisms related to cardiovascular diseases (15, 51). On the other hand, CNHs exert some cardioprotective actions, including (1) decrease in blood pressure; (2) increase in natriuresis and diuresis; and (3) inhibition of both the sympathetic nervous system and the release or action of several hormones, including aldosterone, angiotensin II, endothelins, renin, and vasopressin (16). Kuroski de Bold (51) hypothesized that the lower cardiovascular risk of healthy fertile women compared with men is, at least in part, due to the stimulatory effect of sex female steroid hormones on cardiac endocrine function, in this way virtually opening the search for some pathophysiological mechanisms linking together sex, endocrine function, and cardiovascular risk.

There are only few experimental studies in animal models specifically designed to investigate the influence of sex steroid hormones on cardiac endocrine function (15). These studies have some important limitations: rodents rather than primates, and castrated rather than fertile animals, have been studied. As a consequence, the results of these studies should be applied with extreme caution to healthy fertile men and women. Experimental studies in animals have pointed out that female sex steroids increase ANP gene expression in a dose-dependent manner and that both estradiol and progesterone are necessary to maintain suitable levels of ANP gene expression in rat cardiomyocytes (15). Furthermore, hormone replacement therapy with female steroid hormones shows a stimulatory action on the production/secretion of CNHs in postmenopausal women (46, 61).

As far as the effects of androgens on the production/secretion of CNHs are concerned, the currently available data are still conflicting. Results of experimental studies with atrial cultured myocytes of newborn rats suggested that testosterone stimulates the synthesis and secretion of both ventricular and atrial ANP (65, 66). On the contrary, in another study, performed in castrated male rats, plasma ANP concentration and atrial stores were found to be increased and testosterone replacement was associated with a decrease in plasma ANP concentration, but not in atrial stores (42). In a clinical study, androgen receptor blockade and, to a lesser extent, androgen suppression were found to increase NT-proBNP plasma value in men with prostate cancer (23).

More recently, two large population-based studies have attempted to clarify the role of male sex steroid hormones on the regulation of cardiac endocrine function in humans. The Dallas Heart Study, observed by Chang et al. (9), reported no association between estrogen status and NT-proBNP levels, whereas a strong inverse association was found between measures of free testosterone and NT-proBNP in young women (age range, 35–49 yr). Saenger et al. (76) reported an inverse association of NT-proBNP with serum testosterone, a direct association with sex hormone-binding globulin, and no significant association with circulating levels of estradiol in a large population of girls and boys (age range, from 2 mo up to 18 yr).

The above-mentioned data suggest that female and male sex steroid hormones together contribute to the regulation of production/secretion of CNHs: estrogens may have a stimulatory, whereas androgens a inhibitory, action (15). The interrelationships between CNHs and steroid hormones may be schematically represented by three distinct retroactive mechanisms. In normal cycling women, natriuretic peptides may share an inhibitory action on steroidogenesis, follicular development, granulosa cell maturation, and ovulation, whereas estrogens may have a stimulatory effect on the production/secretion of ANP and BNP production/secretion by cardiomyocytes. Conversely, in adult men, natriuretic peptides may share a stimulatory effect on testis steroidogenesis, whereas androgens may have an inhibitory effect on ANP and BNP production/secretion by cardiomyocytes. Adrenal corticosteroids (including glucocorticosteroids and mineralcorticosteroids) show both direct and indirect stimulating actions on cardiac endocrine function, whereas CNHs inhibit the production of corticosteroids by adrenal gland both directly throughout the specific natriuretic peptide receptors on zona fasciculata and glomerulosa cells of adrenal gland and indirectly by inhibiting the action of renin-angiotensin system. However, although fascinating, this hypothesis needs further evidence. In particular, it should be elucidated whether sex steroids are actually able to affect (increase or decrease) the production/secretion of BNP in mammalian cardiomyocytes both in cell cultures and in vivo (15).

Plasma proBNP May Be a Circulating Precursor of Active BNP Hormone

Cardiac endocrine function has attracted the attention of clinicians when the pivotal role of CNHs in the pathophysiology of HF was established (10, 11, 16, 36, 69). Furthermore, the introduction of the assay of B-type-related natriuretic peptides in clinical practice has resulted in a significant accuracy improvement of the diagnostic and prognostic stratification workup in patients with cardiac diseases (14, 22, 25, 26, 29, 45, 70).

A deficient response of cardiac endocrine function was proposed to explain the altered electrolyte and fluid homeostasis occurring in chronic HF (16). This phenomenon, defined as the “endocrine paradox” of the heart (33, 36), is characterized by extremely high-circulating levels of hormones with powerful diuretic/natriuretic and vasodilator activity in patients with congestive HF, showing signs of fluid retention and vasocostriction. Some recent findings suggest that the posttranslational processing of ventricular proBNP is not efficient in HF patients. As a consequence, the great part of BNPs, assayed in these patients, is devoid of biological activity (11, 34, 58).

In addition to bioactive BNP1–32, a huge numbers of circulating proBNP-derived fragments can be identified by chromatographic procedures in human plasma, including the intact and glycosylated forms of precursor proBNP and NT-truncated BNP form 3–32 (34, 43, 58, 80–83). When compared with inactive peptides proBNP and NT-proBNP, the active peptide BNP has a shorter plasma half-life (~15–20 min vs. 1 or 2 h) and consequently lower plasma concentration (Table 2).
Recent studies demonstrated that the intact or glycosylated forms of proBNP constitute a significant portion of immunoreactive B-type-related peptides circulating in plasma of patients with HF (34, 58, 80–83). According to these findings, it is theoretically conceivable that the active hormone (i.e., BNP) may be produced even in vivo from the circulating intact precursor proBNP through enzymatic cleavage by some plasma proteases (24, 43, 49). Indeed, a very recent study demonstrated that the processing of human proBNP to active BNP can occur in the circulation by means of in vivo in a rat model (81). The above-mentioned studies (11, 34, 43, 58) open a new and more complex scenario regarding the circulating BNP: the intact precursor proBNP might be actually considered a circulating prohormone. This hypothesis assumes that the peripheral processing of circulating proBNP would be submitted to regulatory rules, possibly altered with HF progression.

Resistance to the Biological Effects of CNHs

All natriuretic peptides share a direct diuretic, natriuretic, and vasodilator effect as well as an inhibitory action on the inflammatory processes of both myocardium and smooth muscle cells (19, 40, 62), thus exerting a protective effect on endothelial dysfunction and vascular remodeling (71, 79, 98). These effects are mediated by two different guanylate cyclase-coupled receptors, NPR-A (more specific for ANP and BNP) and NPR-B (more specific for CNP), whereas a third specific receptor NPR-C, not coupled to a guanylate cyclase, essentially has a clearance function for all natriuretic peptides (16).

A blunted natriuretic response after pharmacological doses of ANP and BNP has been observed in experimental models and in patients with chronic HF, suggesting a resistance to the biological effects of CNHs, principally natriuresis (10, 73, 100). As discussed in detail previously (11, 16), resistance to the biological action of CNHs can be attributed at least to three different causes/mechanisms, acting at prereceptor, receptor, and postreceptor levels, respectively (Table 3).

As concerns the prereceptor level, recent studies suggest that in patients with HF, there is an insufficient posttranslational maturation of the biosynthetic precursors of BNP system (i.e., proBNP). An insufficient maturation of proBNP can be caused by an altered processing that may occur before (i.e., within the cardiomyocyte) or after (i.e., in the bloodstream) the secretion of the prohormone (33, 36). Circulating proBNP can be processed in vivo in the human blood by a soluble form of protease corin. Indeed, corin is present in human blood (24), and so this enzyme can process the circulating intact precursors of natriuretic hormones (49). Furthermore, plasma corin levels have been found to be significantly lower in HF patients than in healthy controls with a reduction in the plasma enzyme levels paralleled by the severity of the disease (24). An altered processing of proBNP might represent a possible future therapeutic target, i.e., by developing drugs able to induce the cleavage of the prohormone into the active BNP. Furthermore, the measurement of circulating corin levels may be used as a diagnostic and/or prognostic biomarker of HF (24).

Considering the possible causes of resistance at the receptor level (Table 3), it is theoretically conceivable that an increased expression of the NPR-C in some peripheral tissues can increase the peripheral clearance of CNHs throughout this specific way, thus reducing their circulating levels. It is well known that obese individuals have reduced levels in circulating BNP compared with lean subjects (15, 78). The finding that NPR-C is overexpressed in adipocytes of obese individuals allowed an explanation for these reduced CNH levels in obese subjects (15, 78). Moreover, some gene polymorphisms of specific natriuretic peptide receptors have associated with some cardiovascular diseases, including systemic arterial hypertension (72, 74, 96, 106), cardiomyopathy (103), and stroke (75). However, the true clinical impact of these studies is still debated, considering that the most frequent cardiovascular diseases are polygenic disorders (99).

Finally, at the postreceptor level, an increased activity of the cGMP phosphodiesterase (PDE) V, which metabolizes cGMP, may contribute to increase the resistance to the natriuretic peptide action. The CNHs and NO systems are activated in congestive HF, resulting in an increased synthesis of cGMP, which serves as a second messenger for both humoral systems (88). In severe chronic experimental HF, glomerular cGMP accumulation decreases in response to both ANP and sodium nitroprusside, whereas cGMP- and cGMP-PDE activities are enhanced (88). In vivo, cGMP PDE V inhibition was reported to markedly potentiate the natriuretic response to acute volume expansion, an effect that was attenuated by the administration of a monoclonal antibody directed against ANP (105). Forfia et al. (31) demonstrated that the inhibition of PDE V by sildenafil...
had minimal effects on cardiovascular hemodynamics in healthy dogs; conversely, when sildenafil was administered to HF animals, it exerted similar hemodynamic effects as synthetic BNP, and the combination of BNP and sildenafil was additive in reducing pulmonary pressures. These findings demonstrated that an increased PDE V activity is involved in the pathophysiology of HF, suggesting a novel possible pharmacological target.

Conclusions and Prospective Remarks

A huge number of experimental and clinical studies, published in the first decade of this century, have added further support to the hypothesis that that human heart is a relevant component of a complex network including endocrine, nervous, and immune systems. In particular, novel research fields have been intensively developed with the aim to elucidate the complex interrelationships between cardiac endocrine function, sex steroid hormones, and adipokine systems (15). However, some issues need to be further investigated.

Although fascinating, the hypothesis that gonadal function regulates both body fat distribution and cardiac endocrine function needs further evidence (15). In particular, it is still lacking the conclusive demonstration that sex steroids (especially androgens) are able to actually affect (increase or decrease) the production/secretion of CNHs from mammalian (including human) cardiomyocytes both in cell cultures and in vivo.

Obesity is associated with ectopic lipid deposition even in the heart, which may directly exert a lipotoxic effect on the myocardium by locally secreting several cytokines and adipokines (38). These substances may affect both the endocrine and the contractile function of the cardiomyocytes through a paracrine effect (38). However, the specific role of adipokines in the CNH production/secretion process needs to be further investigated.

These studies will hopefully shed light on the complex, but clinically relevant, interrelationships between cardiovascular risk, sex, and body fat mass and distribution (7, 15, 51).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

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