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M. Emdin, C. Passino, C. Prontera, M. Fontana, R. Poletti, A. Gabutti, C. Mammini, A. Giannoni, L. Zyw, G. Zucchelli and A. Clerico
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Arch Intern Med, June 11, 2007; 167 (11): 1122-1129.

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A. Clerico, M. Fontana, L. Zyw, C. Passino and M. Emdin
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Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications

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Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. *Am J Physiol Heart Circ Physiol* 290: H17–H29, 2006; doi:10.1152/ajpheart.00684.2005.—The discovery of cardiac natriuretic hormones required a profound revision of the concept of heart function. The heart should no longer be considered only as a pump but rather as a multifunctional and interactive organ that is part of a complex network and active component of the integrated systems of the body. In this review, we first consider the cross-talk between endocrine and contractile function of the heart. Then, based on the existing literature, we propose the hypothesis that cardiac endocrine function is an essential component of the integrated systems of the body and thus plays a pivotal role in fluid, electrolyte, and hemodynamic homeostasis. We highlight those studies indicating how alterations in cardiac endocrine function can better explain the pathophysiology of cardiovascular diseases and, in particular of heart failure, in which several target organs develop a resistance to the biological action of cardiac natriuretic peptides. Finally, we emphasize the concept that a complete knowledge of the cardiac endocrine function and of its relation with other neurohormonal regulatory systems of the body is crucial to correctly interpret changes in circulating natriuretic hormones, especially the brain natriuretic peptide.

atrial natriuretic peptide; brain natriuretic peptide; cardiac natriuretic hormones; cardiac function; heart failure; cardiovascular diseases

THE PRESENCE OF SECRETORY GRANULES in mammalian (including human) atrial cells has been known since 1965 (66, 77), but only in 1976 did Marie et al. (102) find that the formation of these granules could be influenced by changes in the hydro-electrolytic balance. From those original observations, De Bold et al. (29) demonstrated in 1981 that intravenous injection of atrial extracts provoked a rapid and massive diuresis and natriuresis in rats.

This seminal study paved the way for the isolation, purification, and identification of a family of natriuretic and vasodilator peptides named atrial natriuretic peptides or factors and more commonly known as ANP or ANF (20, 30, 33, 105, 136). Furthermore, it was demonstrated that not only atrial, but also ventricular, cardiomyocytes can secrete peptides with natriuretic activity, in particular, the brain natriuretic peptide (BNP), so called because first isolated from porcine brain (20, 30, 33, 105, 136). More recently, C-type natriuretic peptide (CNP), mainly produced and secreted by endothelial cells and by central nervous system neurons, and urodilatin, synthesized and secreted by renal cells (and present in urine, but not in plasma), were added to this peptide family (20, 30, 33, 105, 136). Finally, a new peptide, named dendroaspis natriuretic peptide (DNP), was identified in mammalian plasma, but its origin and pathophysiological relevance are still unclear (132).

The scientific impact of these studies was of paramount importance. The discovery of cardiac natriuretic hormones (CNH) by De Bold et al. (29) made it necessary, 25 years later, to completely revise the concept of heart function. Indeed, we should no longer consider the heart only as a pump but rather as a multifunctional and interactive organ, a nodal point in a complex network, and an active component of the integrated systems of the body (including nervous, endocrine, and immune system). It is now clear that the heart exerts also an endocrine function, plays a key role in the regulation of circulation, and hydroelectrolytic homeostasis, and can exchange physiologically relevant information with other organs and systems, which include central and autonomic nervous system, kidney, adrenal glands, vascular endothelium, adipose tissue, and immune system (30, 105). This previously unsuspected cardiac function explains the great pathophysiological and clinical significance that a rapidly growing number of studies is attributing to natriuretic peptides (20). Indeed, cardiac endocrine function should be considered closely related and integrated with other cardiomyocyte properties, such as excitability and contractility. Moreover, this function can be evaluated and measured with methodological approaches and laboratory techniques commonly used for studying and measuring the activity of endocrine glands. Finally, the results of these investigations need to be interpreted in light of classic endocrinological concepts, such as hormone production, metabolism, peripheral action, and specific receptors.

In this review, we will consider a number of studies supporting the hypothesis that an important exchange of infor-

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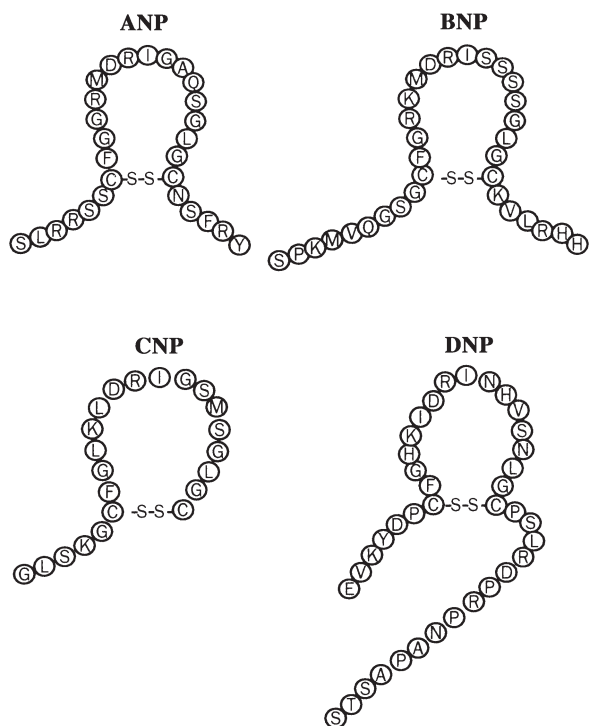


Fig. 1. Peptide chains of the atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP).

mation exists between endocrine and contractile function of the heart. In our opinion, understanding this integration may lead to a more accurate and complete comprehension of cardiac physiology and of the pathophysiology of heart failure. Furthermore, we will discuss a second intriguing hypothesis, i.e., that cardiac endocrine function is an essential component of the integrated systems of the body and thus plays a pivotal role in fluid, electrolyte, and hemodynamic homeostasis. Whereas previous reviews have extensively covered the topic of cardiac hormones, they have not sufficiently emphasized the cross-talk between cardiac endocrine and contractile function and between cardiac endocrine function and other integrated systems of the body. Moreover, the pathophysiological and clinical relevance of these interactions currently have not been discussed in detail. On the basis of such premises, we will first discuss those studies supporting the hypothesis that cardiac endocrine function can better explain some pathophysiological mechanisms acting in myocardial dysfunction, heart failure, and other cardiovascular diseases. Emphasis will be put on the strong and pathophysiologically relevant effects of cardiac natriuretic peptides on peripheral resistance in heart failure. Finally, we will try to provide arguments to support the idea that a complete knowledge of the cardiac endocrine system and of its relations with other neurohormonal regulatory systems of the organism is crucial to interpret correctly measurements of CNH and in particular of BNP.

CHEMICAL STRUCTURE AND SYNTHESIS OF CNH

All CNH share a similar structural conformation, characterized by a peptide ring with a cysteine bridge. This ring remained well preserved throughout the phylogenetic evolu-

tion, because it constitutes the site of the peptidic hormone that binds to its specific receptor. Conversely, the two-terminal amino acid chains (i.e., NH₂ and COOH terminus) show a high degree of variability among the natriuretic peptides in terms of both length and composition (Fig. 1).

The natriuretic peptide genes encode for the precursor sequences of these hormones, named prohormones, which are then splitted into prohormones by proteolytic cleavage of a NH₂-terminal hydrophobic signal peptide. This cleavage occurs cotranslationally during protein synthesis in the rough endoplasmic reticulum before the synthesis of the COOH-terminal part of the prohormone sequence is completed (49). In particular, the human BNP gene encodes for a preproBNP molecule of 134 amino acid residues, including a signal peptide of 26 amino acids (Fig. 2). BNP is cleaved out of a prohormone molecule of 108 amino acids, the proBNP₁₋₁₀₈, usually indicated as proBNP. Before secretion, proBNP is split by proteolytic enzymes into two peptides: the proBNP₁₋₇₆ (NH₂-terminal peptide fragment), usually indicated as NT-proBNP and biologically inactive, and the proBNP₇₇₋₁₀₈ (COOH-terminal peptide fragment), which is the active hormone (BNP).

It is important to note that the preproBNP precursor is not detectable, and its existence is only theoretically deduced from the BNP cDNA sequence of human (or other mammalian) gene. On the other hand, intact proBNP, NT-proBNP, and BNP are identifiable in plasma by chromatography and immunoassay (8, 49, 146, 147). Moreover, ANP and BNP can be produced and costored in the same granule in different stages of peptide maturation (30, 105).

REGULATION OF PRODUCTION/SECRETION OF ANP AND BNP IN CARDIAC TISSUE

ANP and BNP are synthesized and secreted mainly by cardiomyocytes. However, it is believed that ANP is preferentially produced in the atria, whereas BNP is preferentially synthesized in the ventricles and particularly in patients with chronic cardiac diseases. Synthesis and secretion of those two peptides may be differently regulated in atrial versus ventric-

CARDIOMYOCYTE

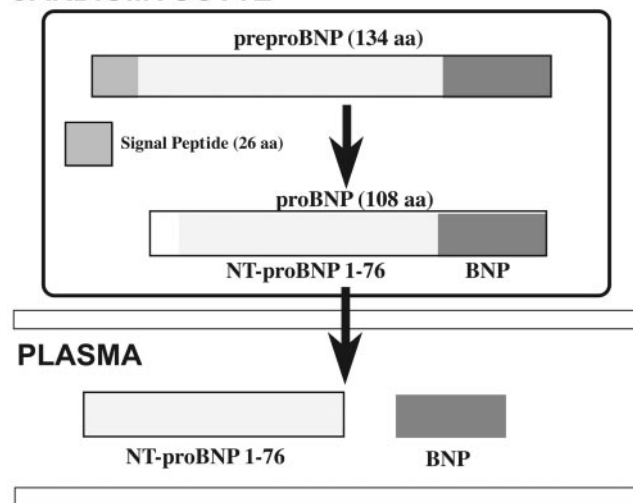


Fig. 2. Schematic representation of production/secretion pathways of BNP and of its precursor peptides.

ular myocytes and, probably, during neonatal versus adult life (30, 31, 105). As a consequence, it is conceivable that two separate cardiac endocrine systems exist, i.e., one in the atrium, where ANP and its related peptides are preferentially produced, and the other in the ventricle, prevalently secreting BNP and its related peptides. Therefore, the acronym CNH will be used in this review only when it is clear that all natriuretic peptides share the same features and actions in a given context. Otherwise, ANP and BNP will be discussed as separate hormones.

It is important to note that more information is available about the mechanisms responsible for the regulation of production/secretion of ANP in atrial cardiomyocytes rather than BNP in ventricular cardiomyocytes. Furthermore, these data were obtained from experimental animals, especially rodents and, to a lesser extent, pigs and sheep. However, some evidence suggests prudence in their use for the interpretation of specific pathophysiological conditions in humans. On the other hand, BNP and its related peptides have been preferentially used for diagnosis, stratification, and monitoring of patients with cardiac and noncardiac diseases during the most recent years, thus more clinical data are available on these peptides than on ANP and its related peptides.

It is likely that most of the circulating ANP and BNP derive from the atria in healthy subjects (105). Some recent data suggested that not only cardiomyocytes, but also fibroblasts, may produce CNH in the human heart (169). It has also been proposed that the endocrine response of the heart to pressure or volume load varies depending on whether the stimulus is acute, subacute, or chronic (30, 105).

Atrial cardiomyocytes store prohormones (proANP and proBNP) in secretory granules and split them into ANP and BNP before secretion. Consequently, cardiac natriuretic hormones seem predominantly secreted throughout a regulated pathway (30, 31, 105). However, there is also the possibility that some ANP is constitutively released by passive diffusion (30, 31, 105). BNP gene is expressed in both atrial and ventricular myocytes of normal and diseased hearts (30, 31, 105, 136).

Ventricular myocytes do not usually display any evident secretory granules at electron microscopy in the normal heart of adult mammals (105). However, some authors identified secretory granules, similar to the atrial ones, in samples of ventricular myocardium collected during surgery or in endocardial biopsies studied by electron microscopy and immunohistochemistry (57, 115). These observations suggest that normal ventricular myocardium may produce only a limited amount of BNP in response to an acute and efficacious stimulation, probably via a constitutive secretory pathway, whereas

the amount of hormone produced and secreted after chronic stimulation could be greatly increased via a secretory pathway that is upregulated in patients with cardiac disease (105).

From a clinical point of view, it is important to note that chronic cardiac dysfunction induces the secretion of a greater amount of BNP rather than ANP, probably because the former is produced mainly by ventricular myocardium, of which its mass is predominant. Moreover, ventricular BNP gene expression can be selectively upregulated during the evolution of diseases affecting the ventricles, as demonstrated experimentally in dogs with pacing-induced congestive heart failure (94). Consistent with these experimental findings, the molar ratio of circulating BNP over ANP increases progressively with the severity of heart failure from a mean value of 0.5 in healthy subjects up to 3 in patients with New York Heart Association (NYHA) functional class IV (Table 1) (20). These data explain why circulating BNP is a better diagnostic index in patients with cardiac disease compared with ANP (20, 22).

MECHANICAL AND CHEMICAL STIMULI

Wall stretch is the most important stimulus for synthesis and secretion of ANP in the atrial walls (30, 31, 105, 136, 145, 152). For this reason, any physiological condition associated with an acute increase in venous return (preload), such as physical exercise, rapid changes from standing to supine position, and head-out water immersion, causes a more rapid augmentation in ANP than in BNP plasma concentration in an adult healthy subject. For instance, changes in ANP and BNP secretion have been well characterized during and after tachyarrhythmia induced in pigs by rapid atrial pacing (225 impulses/min). In this model, ANP plasma concentration shows a sharp initial peak followed by a decline but remains significantly elevated throughout the 24-h postpacing, whereas BNP increases significantly after an 8-h pacing period and even more after a 24-h pacing (129). Also acute changes in the effective plasma circulating volume, for instance, during a dialysis session in patients with chronic renal failure, cause greater variations in circulating levels of ANP than BNP (20).

Wall distension is generally considered the main mechanical stimulus also for BNP production by ventricular tissue. This occurs in conditions characterized by electrolyte and fluid retention, and therefore expansion of effective plasma volume, such as primary or secondary hyperaldosteronism accompanying cardiac, renal, and liver failure (20, 30, 105). However, several studies indicate that BNP production/secretion may be differently regulated in normal compared with diseased ventricular myocardium. Indeed, ventricular hypertrophy and especially the concomitant presence of fibrosis can stimulate

Table 1. BNP and ANP and molar ratio (BNP/ANP) value in normal subjects and patients with heart failure divided according to NYHA functional class

	Normal Subjects	NYHA I	NYHA II	NYHA III	NYHA IV
<i>n</i>	52	35	141	97	39
BNP	4.1 ± 6.1	22.5 ± 34.0	66.6 ± 88.4	131.6 ± 126.3	185.7 ± 169.2
ANP	8.3 ± 5.1	18.6 ± 15.1	37.5 ± 40.6	65.8 ± 65.8	62.0 ± 46.8
Molar ratio	0.5	1.2	1.8	2.0	3.0

Values are means ± SD in pmol/l; *n*, number of subjects. BNP, brain natriuretic peptide; ANP atrial natriuretic peptide; NYHA, New York Heart Association. Unpublished data from the authors' laboratory.

BNP production (30, 31, 105, 141, 156, 181). Furthermore, more recently, experimental and clinical studies indicated that also myocardial ischemia, and perhaps hypoxia, per se, could induce the synthesis/secretion of BNP and its related peptides by ventricular cells, even if isolated and cultured (7, 32, 49, 52, 68, 165). Plasma levels of CNH, especially BNP and its related peptides, were found closely related to aerobic exercise capacity in patients with heart failure (76, 186, 189). In particular, plasma NT-proBNP correlates better with peak oxygen consumption and exercise duration compared with other indexes of left ventricular systolic function, such as ejection fraction (186). These results may explain the elevated levels of BNP found in patients with acute coronary syndrome or during exercise-induced ischemia (43, 138), in the absence of a significant dilatation of ventricular chambers (7, 32), suggesting a neurohormonal activation secondary to both reversible myocardial ischemia or necrosis (68).

HUMORAL STIMULI

Mounting evidence from *in vivo* and *ex vivo* studies is providing support to the hypothesis that the production/secretion of ANP and BNP is regulated by complex interactions with the neurohormonal and immune systems, especially in the ventricular myocardium (105). A summary list of some neurohormones, cytokines, and growth factors, which can affect the production/secretion of ANP and BNP, is reported in Table 2.

Endothelin-1 and angiotensin II are considered the most powerful stimulators of production/secretion of both ANP and BNP (30, 31, 105); similarly, glucocorticoids, sex steroid hormones, thyroid hormones, some growth factors, and cytokines (especially TNF- α , interleukin-1, and interleukin-6) share stimulating effects on the CNH system (30, 31, 35, 54, 61, 85, 95, 97, 105, 156, 160, 187, 188). The finding that CNH production is stimulated by cytokines and growth factors suggests a link between cardiac endocrine activity and remodeling or inflammatory processes in myocardial and smooth muscle cells. A large number of studies have recently contributed to support this hypothesis (35, 48, 55, 59, 61, 76, 78, 95, 141, 151, 156, 160, 181, 187, 188).

More complex, and still in part unknown, is the effect of adrenergic stimulation on CNH production. The α_1 -adrenergic agonist phenylephrine enhances the expression of some transcription factors, such as *Egr-1* and *c-myc*, which regulate (usually increasing) natriuretic peptide gene expression in cultured neonatal rat cardiomyocytes (30, 31, 74, 78, 105, 151,

162). In isolated adult mouse cardiomyocytes, the β -agonist isoproterenol reduced the expression of BNP mRNA but not of ANP, an effect that was prevented by the β_1 -antagonist CGP-20712A (4). Clinical studies performed in hypertensive patients have shown that monotherapy with β -blockers, either β_1 -selective or not, is associated with an increase in the plasma concentration of ANP and/or BNP and their related peptides (53, 114, 123, 171). In contrast, the CNH response can be heterogeneous during β -blocker therapy in congestive heart failure (22, 192) probably due to the various additive effects of other coadministered drugs. Nevertheless, a chronic treatment with β -blockers, resulting in improvement of cardiac function and exercise capacity and reduction in filling pressure and cardiac volumes, is usually associated with a significant fall in BNP and its related peptides in patients with heart failure (22, 44, 157).

As far as hormones more specifically acting on intermediate metabolism are concerned, insulin, but not hyperglycemia alone, increased ANP expression and secretion in cultured rat cardiac myocytes (163). Moreover, in a model of genetic murine dilated cardiomyopathy, short-term treatment with the growth hormone releasing factor improved left ventricular function and significantly limited ANP and BNP gene overexpression in left ventricular tissue (63).

In summary, a conspicuous number of experimental and clinical studies demonstrated that production and secretion of CNH are closely and subtly regulated by mechanical, chemical, neurohormonal, and immunological factors. Thereafter, plasma concentration of CNH can be considered as a sensitive index of the perturbation of the homeostatic systems. It is becoming progressively more evident that ANP and BNP can be diversely regulated under certain pathophysiological conditions. Given the important roles of the BNP in both cardiovascular physiology and pathology, the mechanisms that control expression of this hormone merit further investigation.

BIOLOGICAL ACTION OF CNH

CNH have powerful physiological effects on hemodynamic, body fluids, and electrolyte homeostasis (20, 33, 105, 136). CNH share a direct diuretic, natriuretic, and vasodilator effect and an inhibitory action on inflammatory processes of myocardium and smooth muscle cells (20, 33, 56, 58, 98, 111, 136). Moreover, CNH exert a protective effect on endothelial dysfunction by decreasing shear stress, modulating coagulation and fibrinolysis pathways, and inhibiting platelet activation. According to their anti-inflammatory and antihypertrophic actions, CNH (especially CNP) can also specifically counteract vascular remodeling as well as coronary restenosis postangioplasty processes (19, 108, 130, 156, 159, 190).

CNH share an inhibitory action on neurohormonal and immunological systems and on some growth factors (14, 31, 41, 70, 72, 105, 130, 167, 173, 175, 185). The above-mentioned effects on hemodynamics, body fluid, and electrolyte homeostasis can be explained at least in part by the inhibition of control systems, namely, the sympathetic activation, the renin-angiotensin-aldosterone and/or vasopressin/antidiuretic hormone response, and the endothelins, cytokines, and growth factors release (14, 31, 41, 70, 72, 105, 130, 167, 173, 175, 185).

The hormonal action, shared by plasma ANP and BNP, can be enhanced by natriuretic peptides produced locally in target

Table 2. Summary list of some neurohormones, cytokines, and growth factors affecting the production/secretion of CNH

Angiotensin II
Endothelin-1
Adrenergic agents
Cytokines (IL-1, IL-6, TNF)
Growth and coagulation factors
Insulin
GH
Thyroid hormones
Corticosteroids
Estrogens

CNH, cardiac natriuretic hormone; GH, growth hormone.

tissues. Indeed, endothelial cells synthesize CNP, which in turn exerts a paracrine action on smooth muscle (19, 108, 130, 156, 159, 190).

Moreover, renal tubular cells produce urodilatin, another member of the natriuretic peptide family with powerful diuretic and natriuretic properties (176). ANP, BNP, and CNP genes are also expressed in the central nervous system, where they likely function as neurotransmitters and/or neuromodulators (14, 19, 41, 65, 86, 173, 174). This hypothesis is supported, for instance, by the observation that intranasal ANP acts as central nervous inhibitor of the hypothalamus-pituitary-adrenal stress system in humans (126). Finally, coexpression of CNH and of their receptors was observed in rat thymus cells and macrophages (178, 179), suggesting that CNH may have immunomodulatory and anti-inflammatory functions in mammals (180).

Finally, several studies suggested a major role for CNH in the development of certain systems, including skeleton, brain, and vessels (51, 92, 137, 149, 154, 183). In particular, severe skeletal defects and impaired recovery after vascular and renal injury were observed in CNH transgenic and knockout mice (183). In addition, CNH may play a role in the regulation of proliferation, survival, and neurite outgrowth of cultured neuronal and/or glial cells (183).

RESISTANCE TO BIOLOGICAL ACTION OF CNH

A deficient CNH response was proposed to explain altered electrolyte and fluid homeostasis occurring in chronic heart failure (23). However, this interpretation was challenged when the CNH system was more carefully investigated in experimental animals and in humans (23). Patients with chronic heart failure show increased CNH plasma levels compared with healthy subjects (Table 1). This phenomenon has been recently defined as the “endocrine paradox” of the heart (49), characterized by extremely high circulating levels of hormones with powerful natriuretic activity in patients with congestive heart failure who show physical signs of fluid retention and vasoconstriction due to a relatively poor biological activity of the CNH system.

A blunted natriuretic response after pharmacological doses of ANP and BNP has been observed in experimental models and in patients with chronic heart failure, suggesting a resistance to the biological effects of CNH, principally to natriuresis (18, 25, 80, 140, 193). This resistance syndrome was also demonstrated by measuring ANP turnover rate with radioactive tracers in patients with heart failure (23, 24).

A large number of clinical studies demonstrated that the activation of the neurohormonal system accelerates the left ventricular functional impairment in patients with heart failure (9, 20, 22, 118). Furthermore, drugs that contrast the detrimental effects of the neurohormonal system activation have a key role for the current pharmacological treatment of heart failure. Some of these, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II blockers, β -blockers, and spironolactone decrease the circulating levels of CNH (11, 22, 88, 133), “normalize” their kinetics, and increase their biological activity (23, 24). In other words, the treatment with this type of pharmacological agent decreases the systemic resistance to the biological effects of CNH (23, 24). Indeed, patients with heart failure show a progressive and parallel increase in CNH levels and in some neurohormones and cytokines, which correlates

with the severity of the disease. The maximum increase in plasma BNP values (about 45-fold compared with the average value found in healthy subjects) is significantly higher than that observed for neurohormones, cytokines, and even ANP, in heart failure patients (Table 1 and Fig. 3) (39). However, the response of CNH to increasing levels of disease severity is not linear; it shows a sharp increase in CNH plasma concentration in the early phase of heart failure (NYHA class I–II patients), followed, with the clinical progression of the disease, by a blunted increase (NYHA class III), and finally by a plateau (NYHA class IV). This time course is more evident, especially the blunted and plateau phases, in the response of ANP compared with BNP (Table 1 and Fig. 3). These data confirm that production and secretion of ANP and BNP are differently regulated and that these two peptide hormones may act as components of two separate systems.

Resistance to the biological action of CNH can be attributed at least to three different causes. First, circulating CNH might be, at least in part, inactive. Furthermore, a great fraction of CNH might be inactivated by plasma and tissue proteases before they bind to specific receptors. These two conditions account for all possible mechanisms acting at the prereceptor level. Second, CNH-specific receptors might be downregulated

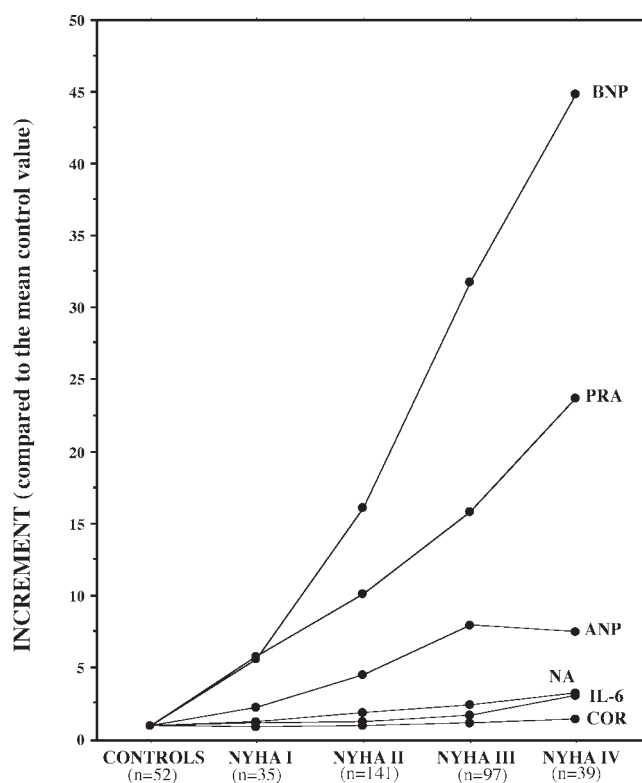


Fig. 3. Mean increases in ANP, BNP, cortisol (COR), IL-6, PRA, and norepinephrin (NE) found in patients with heart failure, divided according to New York Heart Association (NYHA) class. Data obtained from patients were normalized by the mean value found in healthy subjects (controls). Mean (SD) values measured in healthy subjects were the following: ANP, 25.4 ± 15.8 ng/l; BNP, 14.3 ± 20.8 ng/l; PRA, 0.34 ± 0.53 ng·ml⁻¹·h⁻¹; NE, 344.4 ± 134.0 pg/ml; and cortisol, 165.8 ± 48.0 ng/ml. For IL-6, the assay detection limit (i.e., 5 pg/ml) was taken into account to calculate the increases, because all of the normal subjects studied had values below the sensitivity of the assay. Number of subjects/patients studied for each group is reported in parentheses (data modified from Ref. 39).

or desensitized. Finally, some mechanisms might act at postreceptor level by counteracting the biological effects of CNH (Table 3).

Mechanisms acting at prereceptor level. Some peptides, derived in vivo or in vitro from degradation of intact proBNP, are biologically inactive, although they can be measured by immunoassays (20–22, 49). Because the circulating levels of intact proBNP and of its derived peptides increase progressively with the severity of heart failure, immunoassays can greatly overestimate the true biological activity of CNH in patients with severe heart failure (49). Unfortunately, at present, it is not possible to estimate the inaccuracy of CNH immunoassays because these methods use different, not standardized, antibodies and calibrators leading to very variable results (20–22, 49).

CNH are degraded in vivo and in vitro by several types of proteolytic enzymes, including serine-proteases, peptidyl arginine aldehyde proteases, kallikrein-like proteases, and neutral endopeptidases (NEP) (8, 49, 146, 147). Individual differences in the ability of heart tissue to produce their precursors, or of peripheral tissues to degrade CNH, may help to explain some differences in clinical manifestations among heart failure patients with similar severity of ventricular dysfunction (49).

The pathophysiological relevance of mechanisms acting at the prereceptor level is supported by the clinical effects of drugs sharing an inhibitory action on both NEP and ACE (so called vasopeptidase inhibitors), which may share some beneficial effects in patients with arterial hypertension, heart failure, and/or angina pectoris (17, 28, 42, 139, 166). These beneficial effects are mediated by the synergic inhibitory action on ACE and NEP, resulting, respectively, in decreased angiotensin II production and increased circulating levels of CNH due to a reduction in peptide degradation (17, 28, 42, 139, 166). However, a large clinical trial that compared the effects of the vasopeptidase inhibitors omapatrilat to the ACE inhibitor drug enalapril indicated how omapatrilat reduces the risk of death and hospitalization in chronic heart failure but is not more effective than ACE inhibition alone in reducing the risk of a primary clinical event (119).

CNH are small peptides and therefore are freely filtrated by the kidney. Luminal perfusion with ANP has been shown to reduce sodium efflux from the inner medullar collecting duct, suggesting that this hormone has also luminal sites of action

(18, 150). As a consequence, a reduction in the filtration can potentially induce renal hyporesponsiveness to CNH. To date, however, ANP has been detected only on tubular basolateral membranes (18). Thus the mechanisms of CNH luminal action need to be elucidated before conclusions are drawn about the functional significance of reduced natriuretic peptide filtrations in the renal hyporesponsiveness to ANP and other natriuretic peptides.

Mechanisms acting at receptor level. Several studies suggest that the resistance to biological effects of CNH in heart failure may be due, in part, to variations in the relative amount of the three different types of natriuretic peptide-specific receptors. In particular, there could be an upregulation of type C-receptors (NPR-C) with a parallel downregulation of type A- and B-receptors (NPR-A and NPR-B) (6, 83, 110, 168, 170). NPR-A and NPR-B mediate all known hormonal actions of CNH; therefore, their downregulation should induce a deactivation of the CNH system (121, 122). The upregulation of NPR-C receptors that strongly contribute to the clearance of biologically active peptides could further increase the resistance to CNH in patients with heart failure (8). These findings are well in accordance with kinetic studies in patients with heart failure (24, 64). Moreover, a recent report confirmed that the expression of ANP, BNP, and NPR-C receptor were all markedly increased in failing hearts of humans (83). Reversal of cardiomyocyte hypertrophy during left ventricular assist device support was accompanied by normalization of ANP, BNP, and NPR-C mRNA levels and by a significant recovery of responsiveness to ANP (83).

A recent study (40) found that neither NPR-A nor NPR-B were internalized or degraded in response to natriuretic peptide binding in 293T cultured cells, thus suggesting that a downregulation of NPR-A and NPR-B is not the only mechanism for the “inactivation” of CNH action at the receptor level and that other mechanisms may affect the transduction of CNH response at the receptor level in some target tissues. Indeed, another well-characterized deactivation mechanism is the process by which an activated receptor is turned off, commonly referred to as “desensitization” (127). Phosphorylation of the intracellular kinase homology domain of NPR-A and NPR-B is required for hormone-dependent activation of the receptor, whereas dephosphorylation at this site causes desensitization (127). Deactivation of CNH system via desensitization of NPR-A and NPR-B can occur in response to various pathophysiological stimuli (127). Further studies are necessary to clarify what is the most important mechanism of deactivation of the CNH system acting in vivo at the receptor level in patients with heart failure, whether the downregulation (of NPR-A and NPR-B) or the upregulation (of NPR-C) or the desensitization (of NPR-A and NPR-B).

The peripheral resistance to the biological effects of CNH may play an important role in other clinical conditions besides heart failure. For example, NPR-C is also present on cellular membranes of adipocytes. It was suggested that the increase in NPR-C receptors observed in obese subjects can in turn increase the peripheral degradation of CNH and consequently blunt the action of the CNH system (34, 143). Indeed, recent studies have documented decreased circulating levels of CNH in obese subjects compared with age and gender-matched controls (34, 106, 143, 182). In these studies, obesity was assessed only based on body mass index. This reduced activity

Table 3. Classification of possible mechanisms of resistance to biological effects of CNH

Prereceptor level
Presence of inactive peptides in plasma
Increase in inactivation/degradation of active peptides
Upregulation of NPR-C
Increased activity of proteases
Decreased renal filtration
Receptor level
Down-regulation of NPR-A and NPR-B in target tissues
Altered CNH receptor binding or desensitization
Postreceptor level (activated counterregulatory mechanisms)
Altered intracellular signaling
Decreased cGMP cellular accumulation (decreased production or increased degradation)
Altered intracellular pathways downstream cGMP
NPR-A, B, C, natriuretic peptide receptors A, B, C.

of the CNH system may increase the risk of developing arterial hypertension and other cardiovascular diseases due to the noncontrasted and therefore prevailing effects of the sodium-retentive and vasoconstrictive-opposing mechanisms (34, 106, 143, 182). However, this hypothesis needs to be confirmed by studies based on accurate and direct measurements of changes in body fat, rather than total, mass.

Finally, recent studies found that NPR-C receptors could be coupled to a G protein that inhibits cAMP synthesis. These receptors, which are present in great amount especially on the endothelial cell membrane, may mediate some paracrine effects of CNP on vascular tissue (2, 3, 38, 135). Therefore, further studies will be necessary to elucidate the possible role of NPR-C receptors as modulators of CNH action and/or degradation in peripheral tissues.

Mechanisms acting at postreceptor level. There is evidence to support the hypothesis that the activation of the neuroendocrine system can counteract the biological effects of CNH even at postreceptor level. However, at present time, the mechanisms responsible for this resistance at postreceptor level are poorly understood. In particular, little is known about potential alterations of the CNH intracellular signaling pathways in heart failure, and the few published studies have all focused on the second messenger cGMP (18). cGMP levels have been measured and compared with ANP levels. In an early human study, plasma cGMP concentrations increased in proportion to plasma ANP concentrations, suggesting a defect in the signaling pathway downstream cGMP (101). However, renal cGMP production reaches a plateau in more advanced chronic heart failure, despite progressive increase in ANP (101). Similarly, ANP extraction by peripheral vascular bed does not correlate with cGMP production in severe compared with mild chronic heart failure (170). In this pathological condition, renal or peripheral cGMP production may reach a plateau probably because of decreased cGMP generation. However, other mechanisms, such as altered intracellular cGMP turnover, may play a role (18).

Of course, the neuroendocrine system may also indirectly counteract the action of the CNH system on renal function by exerting antinatriuretic properties. This in turn causes reduced Na^+ delivery to the collecting tubules, where CNH exerts its main effects. In fact, the activation of renin-angiotensin-aldosterone axis and of sympathetic nervous and endothelin systems may lead to lower glomerular filtration rate, so limiting CNH tubular effects with sodium and water retention (184).

Because CNH and angiotensin II have renal actions at similar vascular and tubular sites, it has been hypothesized that the renin-angiotensin-aldosterone system could counteract the renal CNH effects, limiting the CNH-induced natriuresis. Moreover, it has been demonstrated in healthy dogs that, at a normal renal perfusion pressure, intrarenal angiotensin II infusion can antagonize ANP-evoked natriuresis (148). Finally, in rats (1) and dogs (177) with aortocaval fistula, 1 wk of ACE inhibition reverses renal unresponsiveness to ANP. On the other hand, sympathetic nerve stimulation provokes afferent and efferent renal arteriolar vasoconstriction and direct Na^+ reabsorption throughout the tubule segments, with a predominant action on the ascending limb of the loop of Henle and, to a lesser degree, on the proximal tubule (18). Also arginine vasopressin peptides, which display antidiuretic actions, and endothelins, powerful vasoconstrictor peptides exerting a wide range of effects in the kidney, may both contribute to renal

hyporesponsiveness to CNH in heart failure patients (18). However, further studies are necessary to better clarify the cellular mechanisms responsible for this action.

In summary, several mechanisms occurring at prereceptorial, receptorial, and postreceptorial levels may play a role in the peripheral resistance to the biological effects of CNH during heart failure. The increased natriuresis and the other beneficial effects induced by drugs inhibiting the action of counterregulatory systems (such as ACE inhibitors, angiotensin II-receptor antagonists, and β -blocker agents) in patients with heart failure suggest that the overwhelming activation of these systems may be considered the predominant pathophysiological mechanism of CNH resistance, probably at postreceptorial level. Unfortunately, the effects of the counterregulatory system on downregulation and/or desensitization of natriuretic peptide receptors are presently not well understood.

From a clinical point of view, it is important to underline that the marked resistance to CNH action may also explain why the administration of CNH analogues (such as nesiritide) did not seem to have more efficacy than the conventional treatment in patients with decompensated congestive heart failure (146). Indeed, according to the hypothesis of CNH resistance, an increase in circulating levels of biologically active hormones (obtained by the inhibition of NEP or by nesiritide infusion) can be useful only if there is a significant decrease in the activation of counterregulatory system, as occurs, for example, during concomitant administration of ACE inhibitors, angiotensin II-receptor antagonists, and/or β -blocker agents. The net effect is a reduced resistance at postreceptor level or an enhanced stimulation of NP-A and NP-B receptors, which induces a reduced resistance at receptor level. A combination of these two beneficial effects is also possible. Finally, the data so far discussed also suggest that monitoring the degree of systemic resistance to the biological effects of CNH could be clinically useful in the follow-up of patients with heart failure.

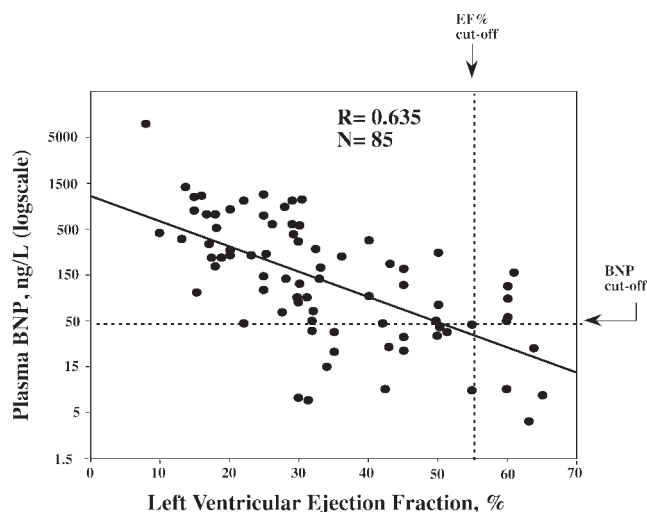


Fig. 4. Close linear relationship between the logarithmic transformation of plasma BNP concentration (y-axis), measured by an immunoradiometric assay method, and left ventricular ejection fraction (x-axis), assessed by nuclear angiography, in patients with cardiovascular diseases (unpublished data from authors' laboratory).

PATHOPHYSIOLOGICAL AND CLINICAL IMPLICATIONS

The literature reviewed so far strongly supports the hypothesis that CNH are active components of the integrated network that includes nervous, endocrine, and immune system. According to this hypothesis, the heart should no longer be considered only as a passive automaton driven by nervous, endocrine, or hemodynamic inputs but as a leading actor on the stage. Therefore, CNH, together with other neurohormonal factors, regulate cardiovascular hemodynamics as well as fluid and electrolyte homeostasis and probably modulate the inflammatory response in some districts, including the cardiovascular. This hypothesis implies that there are two opposing systems in the body: one has sodium-retaining, vasoconstrictive, thrombolytic, proinflammatory, and prohypertrophic actions, whereas the second one promotes natriuresis and vasodilatation and inhibits thrombosis, inflammation, and hypertrophy. CNH are the main effectors of the latter system and work in concert with NO, some prostaglandins, and other vasodilator peptides. Under physiological conditions, the effects of these two systems are well balanced via feedback mechanisms and result in a beat-to-beat regulation of cardiac output and blood pressure in response to endogenous and exogenous stimuli. In patients with cardiovascular diseases, the action of the first system predominates and constitutes initially a compensatory mechanism that progressively leads to detrimental effects.

The knowledge so far accumulated regarding CNH suggests that a continuous and intense information exchange flows from the endocrine heart system to nervous and immunological systems and to other organs, including kidney, endocrine glands, liver, adipose tissue, immunocompetent cells, and vice versa. From a pathophysiological point of view, the close link between CNH system and counterregulatory systems could explain the increase in circulating levels of CNH in some noncardiac-related clinical conditions. Increased or decreased BNP levels were frequently reported in acute and chronic respiratory diseases (5, 82, 90, 91, 96, 112, 128, 161), some endocrine and metabolic diseases (10, 12, 15, 45, 67, 79, 87, 117, 125, 144, 153, 155), liver cirrhosis (60, 89, 142), renal failure (103, 176), acute (septic shock) and chronic inflammatory diseases (13, 16, 62, 120, 158, 187, 191), subarachnoid hemorrhage (46, 84, 104), and some paraneoplastic syndromes (69, 100, 107). Furthermore, elevated BNP levels reveal an endocrine cardiac response to "stress" that does not necessarily originate from the heart itself. In fact, recent studies reported that plasma BNP concentration is an independent risk factor for mortality (cardiac and/or total) in pulmonary embolism (81, 82, 161) and hypertension (112), renal failure (103, 176), severe sepsis (13, 16), amyloidosis (120), sarcoidosis (191), and diabetes mellitus (12). Increased BNP levels in these noncardiac diseases are a useful indication for the clinician that the heart is under stress.

The interrelationships between CNH system and proinflammatory cytokines suggest that cardiac hormones play an important role in mechanisms responsible for cardiac and vascular adaptation, maladaptation, and remodeling in response to various physiological and pathological stimuli (48, 99, 141, 181).

Very small changes in some neurohormones and cytokines can produce wider variations in BNP circulating levels (39) (Fig. 3). On the other hand, changes in hemodynamic param-

eters and plasma CNH levels are closely related in patients with cardiovascular diseases (Fig. 4) (20, 22, 27, 36, 93, 109, 116, 124). However, correlations between plasma CNH levels and parameters such as left ventricular ejection fraction, myocardial mass, and chamber volumes are usually less tight in the general population (large community-based sample, including healthy subjects with or without individuals with asymptomatic myocardial dysfunction) (71, 113, 131, 172). For example, in our laboratory the coefficient of correlation R between left ventricular ejection fraction and BNP in 38 healthy adult subjects without any clinical and echocardiographic evidence of heart failure (mean age 57.3 yr, range 35–78 yr) was only 0.068. Furthermore, a recent meta-analysis demonstrated that the diagnostic significance of BNP levels was higher when clinical criteria were used as reference (gold) standard rather than the echocardiographic examination alone (including the criterion of left ventricular ejection fraction of 40% or less) (37).

These data strongly indicate that the circulating BNP should be better considered as an index of activation of the neuroendocrine system rather than a marker of myocardial dysfunction. The activation or deactivation of the CNH system is almost always the resultant of one or more physiological or pathological changes. For this reason, the results of CNH assays must be interpreted by taking into account clinical history and examination, as well as laboratory and instrumental tests. Of course, the great number of pathophysiological mechanisms that can affect the CNH system renders it sometimes difficult for clinicians to recognize the cause(s) of variations in its activity. On the other hand, CNH measurements add a complementary information to other instrumental and investigative tests. We believe that CNH assays should be considered as an intellectual spur for the search of pathophysiological mechanisms that can satisfactorily explain the measured variations in hormone concentrations.

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