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Atrial Natriuretic Peptide in Heart Failure

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Atrial natriuretic peptide is a peptide hormone of cardiac origin, which is released in response to atrial distension and serves to maintain sodium homeostasis and inhibit activation of the renin-angiotensin-aldosterone system. Congestive heart failure is a clinical syndrome characterized by increased cardiac volume and pressure overload with an inability to excrete a sodium load, which is associated with increased activity of systemic neurohumoral and local autocrine and paracrine mechanisms. Circulating atrial natriuretic peptide is greatly increased in congestive heart failure as a result of increased synthesis and release of this hormone. Atrial natriuretic peptide has emerged as an important diagnostic and prognostic serum marker in congestive heart failure. In early heart failure, it may play a key role in preserving the compensated state of asymptomatic left ventricular dysfunction. Despite increased circulating atrial natriuretic peptide in heart failure, the kidney retains sodium and is hyporesponsive to exogenous and endogenous atrial natriuretic peptide. The mechanism for the attenuated renal response is multifactorial and includes renal hypoperfusion, activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Therapeutic strategies to potentiate the biologic actions of atrial natriuretic peptide may prolong the asymptomatic phase and delay progression to overt congestive heart failure.

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It is now well established that the heart is an endocrine gland that synthesizes and releases the peptide hormone atrial natriuretic peptide. The work of Kisch (1) first suggested such a role for the heart with the observation of membrane-bound storage granules, referred to as specific granules in atrial cardiocytes. The density of these granules was reported to be affected by various experimental procedures, such as changes in fluid and electrolyte balance (2). The physiologic significance of these atrial granules was established when de Bold et al. (3) observed in their seminal study a natriuretic and hypotensive effect in response to intravenous injection of atrial extracts into rats. These hallmark investigations led to the characterization of atrial natriuretic peptide as a 28-residue C-terminal peptide derived from a 126–amino acid precursor pro-atrial natriuretic peptide that is the principal storage form (4). Repeated studies (5–7) have demonstrated that atrial natriuretic peptide possesses unique biologic actions that include natriuretic, vasodilator, renin- and aldosterone-inhibiting and antimitogenic actions.

Although the cellular mechanism for atrial natriuretic peptide synthesis and processing continues to emerge, Edwards et al. (8) have shown, in an elegant study creating cardiac tamponade in animals, that atrial stretch is the principal stimulus for atrial natriuretic peptide secretion. Cardiac tamponade produced a balanced increase in intra-atrial and pericardial pressures with no change in atrial transmural pressure or atrial stretch. No change in circulating atrial natriuretic peptide was observed. In contrast, great artery constriction resulted in increased transmural pressure and atrial stretch in association with elevated plasma atrial natriuretic peptide concentrations. This mechanism explains release of this hormone evoked by a variety of maneuvers and conditions associated with central volume overload (9–11). The cellular mechanism underlying stretch-mediated atrial natriuretic peptide release is dependent on an increase in cytosolic calcium with activation of the phosphoinositide pathway (12).

Two receptors that interact with atrial natriuretic peptide have been identified (13). A biologically active receptor termed the ANPR-A receptor is linked to the activation of particulate guanylate cyclase. Binding of atrial natriuretic peptide to this receptor results in an increase in guanosine 3′,5′-cyclic monophosphate (cyclic GMP), which leads to the biologic actions of atrial natriuretic peptide in many tissues. The most abundant receptor for atrial natriuretic peptide, however, is a biologically silent clearance receptor termed the ANPR-C receptor, which functions to bind and clear atrial natriuretic peptide from the circulation (14). After binding, receptor-mediated endocytosis occurs with intracellular degradation.

Congestive heart failure represents a state in which cardiac synthesis and release of atrial natriuretic peptide exceed those of all other states (Fig. 1). In this brief review, we will attempt to provide an update on important issues regarding atrial natriuretic peptide in congestive heart fail-

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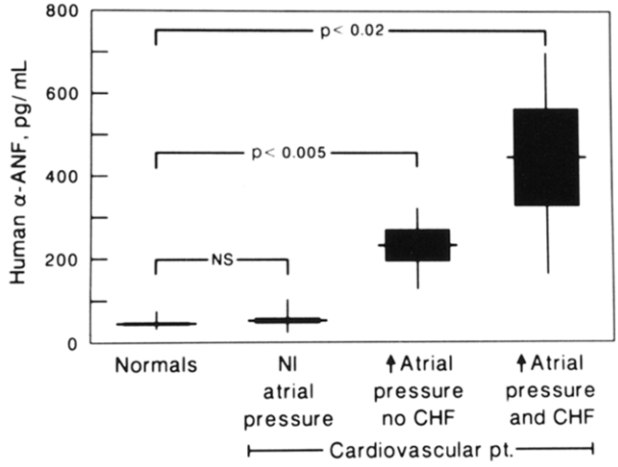

Figure 1. Plasma concentrations of atrial natriuretic peptide (ANF) in normal humans and three groups of patients (pt.) with cardiovascular disease. Normal (NI) atrial pressure, and increased atrial pressure without or with congestive heart failure (CHF) are shown. Reprinted, with permission, from Burnett et al. (24).

ure, with a focus on its biologic role in asymptomatic left ventricular dysfunction, mechanisms of atrial natriuretic peptide hyporesponsiveness in severe heart failure, cardiac synthesis in heart failure, diagnostic and prognostic significance of natriuretic peptide in heart failure and a novel therapeutic strategy of employing endogenous atrial natriuretic peptide in the treatment of heart failure by inhibiting its enzymatic degradation.

Functional Role of Atrial Natriuretic Peptide in Early Heart Failure and Mechanisms of Hyporesponsiveness in Severe Heart Failure

Several well designed therapeutic trials (15–18) have demonstrated drug efficacy in improving functional capacity and survival. The fact that patients classified in New York Heart Association functional class I or II experienced significant benefit and that drug intervention was not completely effective in halting the progressive worsening process leading to death (16) has shifted an interest to patients in early stages of heart failure. The National Institutes of Health–sponsored Studies of Left Ventricular Dysfunction (SOLVD) (19) in patients with chronic left ventricular dysfunction but without signs of overt heart failure (that is, asymptomatic left ventricular dysfunction) demonstrated humoral activation that is characterized by an increase in circulating atrial natriuretic peptide without activation of the circulating renin-angiotensin-aldosterone system in the absence of diuretic treatment. The known biology of the atrial natriuretic peptide system suggests this cardiac peptide may play a key role in preserving this compensated state of asymptomatic left ventricular dysfunction.

Atrial natriuretic peptide and asymptomatic left ventricular dysfunction. Evidence supports an important role for atrial natriuretic peptide in asymptomatic left ventricular dysfunction to preserve cardiorenal homeostasis, contribute to the maintenance of sodium balance and inhibit activation of the renin-angiotensin-aldosterone system despite ventricular dysfunction. Such a conclusion is supported by a number of key observations. In a low atrial natriuretic peptide model of acute congestive heart failure produced by thoracic inferior vena cava constriction that is characterized by decreased cardiac output without increases in atrial pressures or atrial natriuretic peptide, marked sodium retention, vasoconstriction and activation of the renin-angiotensin-aldosterone system resulted. These findings were not observed in a high atrial natriuretic peptide model produced by rapid ventricular pacing despite similar reductions in cardiac output and mean arterial pressure (20). Exogenous administration of atrial natriuretic peptide in dogs with caval constriction to mimic circulating concentrations encountered in a high atrial natriuretic peptide model of heart failure prevented sodium retention, vasoconstriction and activation of the renin-angiotensin-aldosterone system (Fig. 2). Margulies et al. (21) observed significant natriuresis and renal cyclic GMP generation with elevation of plasma atrial natriuretic peptide after the onset of ventricular dysfunction. Awazu et al. (22) tested the effect of anti–atrial natriuretic peptide antibodies in a model of chronic congestive heart failure in rats. Bolus injection of atrial natriuretic peptide–neutralizing antibodies resulted in further sodium retention without affecting systemic blood pressure or glomerular filtration rate. More recently, Redfield et al. (23) reported on cardiorenal function in a conscious canine model of asymptomatic left ventricular dysfunction. This model mimics the humoral profile of patients with asymptomatic left ventricular dysfunction reported in SOLVD and was characterized by significant ventricular dysfunction without sodium retention in association with elevated atrial natriuretic peptide and no activation of the renin-angiotensin-aldosterone system. In response to acute intravascular volume expansion, normal release of atrial natriuretic peptide and an intact renal natriuretic response were observed. These investigators concluded that increased atrial natriuretic peptide is a marker for cardiac volume overload in early congestive heart failure and contributes to the maintenance of sodium balance and inhibition of the renin-angiotensin-aldosterone system in asymptomatic left ventricular dysfunction. They speculated that therapeutic strategies that potentiate the biologic actions of atrial natriuretic peptide may prolong the asymptomatic phase of ventricular dysfunction and delay progression to overt congestive heart failure.

Renal hyporesponsiveness to atrial natriuretic peptide in overt congestive heart failure. Severe congestive heart failure is a syndrome characterized by sodium retention and activation of the renin-angiotensin-aldosterone system with elevation of circulating atrial natriuretic peptide (24,25). Humans and animal models of chronic congestive heart failure are characterized by an attenuated natriuretic response to endogenous and exogenous atrial natriuretic pep-

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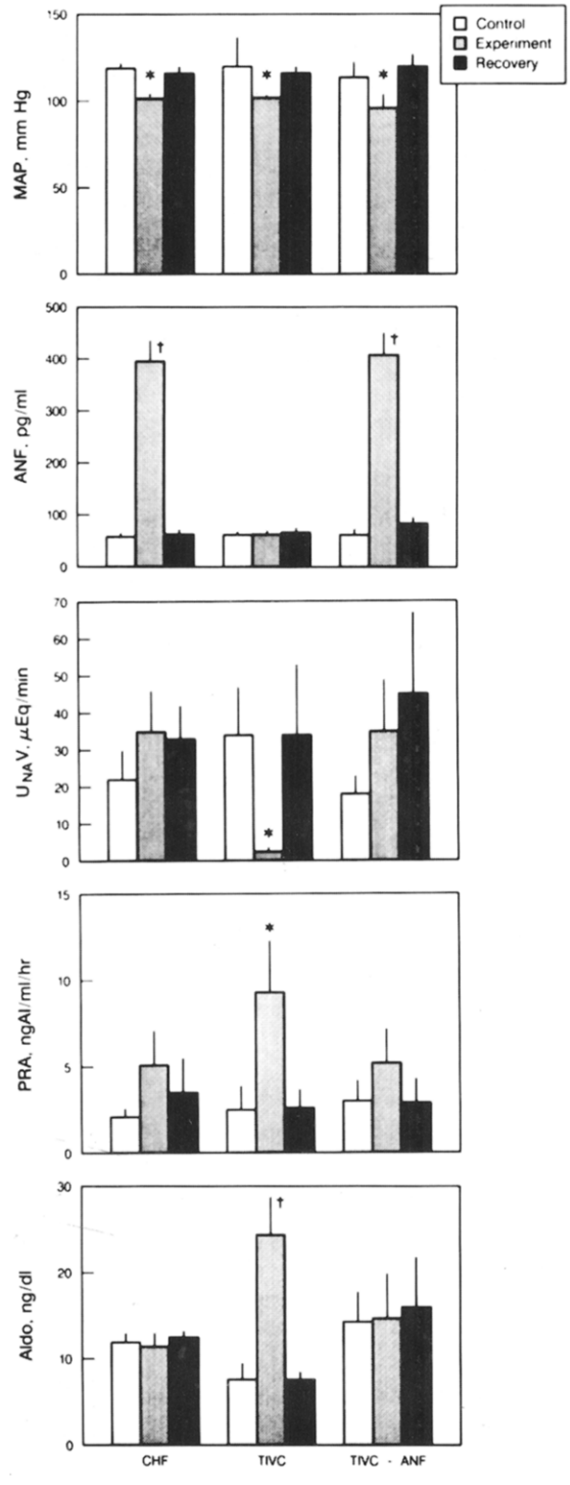
Figure 2. Effect of rapid right ventricular pacing-induced congestive heart failure (CHF), thoracic vena caval constriction and thoracic vena caval constriction (TIVC) plus exogenous atrial natriuretic peptide (TIVC + ANF) on mean arterial pressure (MAP), plasma atrial natriuretic peptide, urinary sodium excretion ($U_{Na}V$), plasma renin activity (PRA) and plasma aldosterone (Aldo). *p < 0.05 experiment or recovery vs. control; †p < 0.01 experiment or recovery vs. control. All data are expressed as mean value ± SEM. Reproduced, with permission, from Lee et al. (20).



tide (21,26–29). It has been suggested that the diminished renal response to the hormone plays an important role in the pathophysiology of sodium retention and systemic and renal vasoconstriction observed in overt heart failure. The mechanisms responsible for the renal hyporesponsiveness to atrial natriuretic peptide in congestive heart failure are most likely multifactorial and include a decrease in renal perfusion pressure (29), increased activity of functional antagonists to atrial natriuretic peptide such as the renin-angiotensin-aldosterone system (30), renal sympathetic nerve activity (31) and circulating noradrenaline (32), atrial natriuretic peptide receptor downregulation (33) and possibly enhanced enzymatic degradation of atrial natriuretic peptide (34).

Increased activity of the renin-angiotensin-aldosterone system plays a key role in mediating the blunted renal response to atrial natriuretic peptide in overt congestive heart failure. The natriuretic response to exogenous atrial natriuretic peptide in salt-retaining rats with chronic arteriovenous fistula could be restored with long-term treatment with the angiotensin-converting enzyme inhibitor enalapril (35). This response occurred despite a decrease in mean arterial blood pressure and was unrelated to changes in endogenous levels of atrial natriuretic peptide. The mechanism of this enhancement is probably complex and includes a reduction in renal vascular resistance, a decrease in angiotensin II that may have opposing actions on the kidney as compared with atrial natriuretic peptide and decreases in cyclic GMP phosphodiesterase activity that are activated by angiotensin II. Indeed, the opposing action of angiotensin II on atrial natriuretic peptide is importantly supported by the work of Showalter et al. (30), who observed a blunting of the natriuretic effect to systemically administered atrial natriuretic peptide when angiotensin II was infused through the renal artery at a dose without systemic effects, indicating that at normal renal perfusion pressure, intrarenal angiotensin II can antagonize the natriuretic response to atrial natriuretic peptide.

Wong et al. (36) demonstrated that renal cyclic GMP production is the principal mediator of the increase in urinary cyclic GMP after administration of exogenous atrial natriuretic peptide in normal rats. Results from our laboratory (21) indicate that sodium retention during the evolution of congestive heart failure occurs in association with a loss of the previously enhanced renal generation of cyclic GMP and with activation of the renin-angiotensin-aldosterone system. In cultured vascular smooth muscle cells, Smith and Lincoln (37) observed that angiotensin II decreased atrial natriuretic peptide-stimulated intracellular cyclic GMP accumulation by stimulating cyclic GMP hydrolysis. This augmented hydrolysis of cyclic GMP appeared to be mediated by calcium-activated cyclic GMP phosphodiesterase. Studies (38) have demonstrated that cyclic GMP phosphodiesterase inhibition markedly potentiates the effect of acute volume expansion and low dose atrial natriuretic peptide infusion on urinary sodium and cyclic GMP excretion, an effect that was attenuated by administration of a monoclonal

antibody directed against atrial natriuretic peptide. These studies support an important role of renal cyclic GMP phosphodiesterase modulation for the biologic response to endogenous and exogenous atrial natriuretic peptide and a key role for angiotensin II in this alteration.

Cardiac Synthesis of Atrial Natriuretic Peptide in Congestive Heart Failure

A hallmark of acute and chronic congestive heart failure is the elevation of circulating atrial natriuretic peptide levels (20,24). This elevation is secondary to enhanced cardiac synthesis and release, which are activated by increased cardiac volume and pressure overload. Recent investigations (39) also support the role of humoral stimulation of atrial natriuretic peptide synthesis and release by other local and circulating humoral factors. In acute congestive heart failure, the increase in circulating atrial natriuretic peptide is secondary to release of stored atrial atrial natriuretic peptide, with enhanced cardiac synthesis maintaining elevated levels with more sustained ventricular failure (40). In the cardiomyopathic strain of Syrian hamster, the content of atrial natriuretic peptide granules within the cardiac atria varies inversely with the circulating plasma level of atrial natriuretic peptide consistent with increased atrial synthesis and release (41). It is possible that the synthetic capacity of the atria is overwhelmed relative to the demands of the system, leading to a state of relative deficiency with chronic and severe ventricular dysfunction. Indeed, in dogs with chronic congestive heart failure, Redfield et al. (42) demonstrated an impaired capacity to release atrial natriuretic peptide in response to acute volume expansion with increases in atrial pressures. Recently, Volpe et al. (43) also observed impaired release of atrial natriuretic peptide in humans with dilated cardiomyopathy and mild congestive heart failure. Thus, a relative deficiency may occur in chronic congestive heart failure with biologic consequences.

Congestive heart failure in humans and animals is characterized by the presence of ventricular atrial natriuretic peptide (44). Because ventricular atrial natriuretic peptide is present in primitive organisms, the occurrence in higher species might represent the reactivation of fetal genes (45). Protooncogenes that regulate the hypertrophic process in cardiomyopathy may also control the recruitment of ventricular atrial natriuretic peptide synthesis (46). It has been shown in cardiomyopathic hamsters that ventricular myocardium becomes the principal source of atrial natriuretic peptide (47).

A portion of total atrial immunoreactive atrial natriuretic peptide in the severely failing human heart is composed of beta-atrial natriuretic peptide, an antiparallel dimer with reduced biologic activity (48). In studies from our laboratory, Wei et al. (49) reported that this altered biologic form of atrial natriuretic peptide is also elevated in the circulation of patients with severe congestive heart failure. Thus, beta-atrial natriuretic peptide exists in overt heart failure and may have biologic significance for this sodium-retaining and vasoconstrictive state.

Diagnostic and Prognostic Role of Circulating Atrial Natriuretic Peptide in Congestive Heart Failure

Because of its elevation in chronic congestive heart failure (24), circulating atrial natriuretic peptide has emerged as an important diagnostic and prognostic serum marker in this condition. Repeated studies have demonstrated that elevated atrial natriuretic peptide correlates with the functional class of symptomatic congestive heart failure. Gottlieb et al. (50) reported that atrial natriuretic peptide provides prognostic data on survival, ventricular ectopic activity and hemodynamic abnormalities. Davis et al. (51) extended these findings and identified atrial natriuretic peptide as a specific and sensitive test for predicting the development of congestive heart failure in elderly subjects. These investigators reported that atrial natriuretic peptide could identify patients at risk for congestive heart failure, suggesting that it could be used in these patients for prevention, early detection and treatment.

We and others have recently focused on the N terminus of pro-atrial natriuretic peptide (N-ANP) which is the nonbiologically active fragment of the prohormone and coreleased with the biologic active 28-amino acid C-terminal (C-ANP). Because N-ANP is cleared more slowly, it circulates at higher concentrations than the biologically active C-ANP. Moreover, it is more stable in vitro than C-ANP (52). In recent studies (53), we examined its specificity and sensitivity as a diagnostic test in identifying subjects with asymptomatic left ventricular dysfunction as documented prospectively with radionuclide angiography and clinical characterization. These studies demonstrated that N-ANP was elevated consistently in patients in New York Heart Association functional class I with asymptomatic left ventricular dysfunction and was more sensitive and specific than C-ANP, thus emerging as an important noninvasive serum marker in the identification of patients with asymptomatic left ventricular dysfunction. The diagnostic importance of N-ANP is also underscored by Hall et al. (52), who recently reported that N-ANP is the most powerful independent prognostic indicator in patients with asymptomatic left ventricular dysfunction after acute myocardial infarction.

Inhibition of Atrial Natriuretic Peptide Degradation in the Therapeutics of Congestive Heart Failure

Since the discovery of atrial natriuretic peptide, strategies have emerged to utilize this peptide in the treatment of disorders of cardiorenal function such as congestive heart failure. Therapeutic strategies have included infusion of the

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peptide and potentiation of its actions by inhibitors of cyclic GMP phosphodiesterase (54,55). Recent therapeutic approaches have focused on inhibition of neutral endopeptidase 24.11, the enzyme that degrades atrial natriuretic peptide.

Two pathways for atrial natriuretic peptide metabolism are enzymatic clearance by means of the ectoenzyme neutral endopeptidase 24.11 and receptor clearance by means of the clearance receptor. Neutral endopeptidase 24.11 is a well characterized ectoenzyme that is present in numerous tissues, including kidney, lung, brain and endothelial cells. Repeated studies have demonstrated that atrial natriuretic peptide is a substrate for neutral endopeptidase 24.11. On the basis of the high concentration of neutral endopeptidase 24.11 in renal brush border membranes, Kenny and Stephenson (56) suggested that renal tubular neutral endopeptidase 24.11 serves a physiologic function of rapidly and efficiently degrading filtered atrial natriuretic peptide to prevent biologically intact peptide from reaching the terminal nephron, which is a major site of action. Evidence also suggests that neutral endopeptidase 24.11 activity may be regulated. Such a phenomenon may be relevant to disease states such as congestive heart failure in which increased neutral endopeptidase 24.11 activity could attenuate the full biologic actions of elevated endogenous atrial natriuretic peptide. This concept may be relevant to congestive heart failure, in which some studies (34) support increased neutral endopeptidase 24.11 activity.

In acute experimental congestive heart failure, we (57) found a parallel increase in urinary cyclic GMP excretion and urinary sodium excretion after neutral endopeptidase inhibition together with an increase in urinary atrial natriuretic peptide, suggesting that delivery of atrial natriuretic peptide to the terminal nephron indeed may activate cyclic GMP and contribute to a natriuretic response. This supports the conclusion that neutral endopeptidase 24.11 may limit the full natriuretic action of elevated endogenous atrial natriuretic peptide in congestive heart failure. Such observations are also supported by studies (58) demonstrating a luminal action of atrial natriuretic peptide in the inner medullary collecting duct to inhibit sodium transport. In chronic experimental congestive heart failure, neutral endopeptidase 24.11 inhibition produces a decrease in atrial pressures and an initial maintenance of cardiac output (34). Neutral endopeptidase 24.11 inhibition potentiated the natriuretic action of endogenous atrial natriuretic peptide by a mechanism independent of systemic or renal hemodynamics. More striking, this natriuretic action occurred in a model of severe congestive heart failure that was resistant to the natriuretic action of exogenous atrial natriuretic peptide, underscoring the potential efficacy of this form of therapy. The observed biologic responses in these studies in acute and chronic experimental congestive heart failure were also greater than that predicted from any increase in circulating atrial natriuretic peptide, indicating a local tissue potentiation of atrial natriuretic peptide (Fig. 3). The unique natriuretic action of neutral endopeptidase 24.11 inhibition may also be associated with cardiovascular and humoral effects. Recently, Elsner et al. (59) reported that long-term neutral endopeptidase 24.11 inhibition in humans with chronic congestive heart failure resulted in favorable hemodynamic responses together with suppression of vasoconstrictor humoral systems.

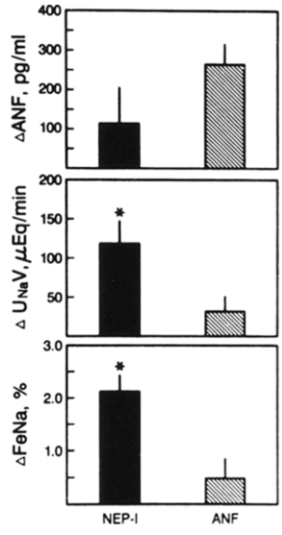

Figure 3. Bar graphs of peak changes in plasma atrial natriuretic peptide (ANF), urinary sodium excretion ($U_{Na}V$) and fractional excretion of sodium (FENa) in congestive heart failure with neutral endopeptidase inhibitor (NEP-I) (30 mg/kg), followed by neutral endopeptidase inhibitor (60 mg/kg) or with exogenous atrial natriuretic peptide (100 ng/kg/min). *$p < 0.05$ neutral endopeptidase inhibitor group vs. atrial natriuretic peptide group. All data are expressed as mean value ± SEM. Reproduced, with permission, from Cavero et al. (34).

We have already discussed the antagonism of atrial natriuretic peptide by the renin-angiotensin-aldosterone system. Such antagonism is also observed in severe congestive heart failure to limit the full natriuretic action of neutral endopeptidase 24.11 inhibition (60). Long-term angiotensin antagonism with angiotensin-converting enzyme inhibition potentiated both the renal hemodynamic and excretory response to neutral endopeptidase 24.11 inhibition, an effect that was abolished by intrarenal infusion of low dose angiotensin. These results support the concept that coinhibition of both neutral endopeptidase 24.11 and angiotensin-converting enzyme may emerge as a unique form of therapy in the treatment of congestive heart failure. Indeed, in light of the knowledge of the delay in onset of symptoms with angiotensin-converting enzyme inhibition in asymptomatic left ventricular dysfunction, one could speculate that coinhibition of both these ectoenzyme systems may emerge as optimal therapy in delaying the onset of overt congestive heart failure.

Future Areas of Atrial Natriuretic Peptide Research in Heart Failure

Despite great advances in our understanding of atrial natriuretic peptide during the last decade, this field of

research is still in its infancy. During the last 3 years, two additional structurally related peptides, brain natriuretic peptide and C-type natriuretic peptide, have been identified. All three natriuretic peptides are separate gene products (13). Brain natriuretic peptide like atrial natriuretic peptide is of cardiac origin and together function as a dual natriuretic peptide system (61). C-type natriuretic peptide, not to be confused with the C-terminal atrial natriuretic peptide, is of endothelial origin and functions as a paracrine factor in the control of vascular tone (62–65). These natriuretic peptides function by means of a family of receptors, which in addition to being localized in endothelial cells, vascular smooth muscle cells and renal epithelial cells are also expressed in the myocardium (13,66). In congestive heart failure, brain natriuretic peptide and atrial natriuretic peptide are elevated in the plasma (61). Although C-type natriuretic peptide is present in human plasma, its activity in congestive heart failure remains undefined (64).

The potential of manipulating these peptides as natriuretic and vasoactive factors will be a major area of research not only in congestive heart failure but in other cardiovascular disease states. Specifically, inhibition of the degradation of the natriuretic peptides may emerge as a key treatment of congestive heart failure either as single therapy or combined with inhibition of the renin-angiotensin-aldosterone system. In summary, our understanding of natriuretic peptides should continue to grow during the 2nd decade after the discovery of atrial natriuretic peptide and the role of the heart as an endocrine organ.

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