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Rationale and Therapeutic Opportunities for Natriuretic Peptide System Augmentation in Heart Failure

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Abstract The natriuretic peptide system (NPS) is intimately involved in cardiorenal homeostasis in health, and dysregulation of the NPS plays an important role in the pathophysiology of heart failure (HF). Indeed, the diuretic, vasorelaxation, beneficial remodeling, and potent neurohumoral inhibition of the NPS support the therapeutic development of chronic augmentation of the NPS in symptomatic HF. Further, chronic augmentation of the protective NPS and in early stages of HF may ultimately prevent the progression of HF and reduced subsequent morbidity and mortality. In the current manuscript, we review the rationale for as well as previous and current efforts aimed at chronic therapeutic augmentation of the NPS in HF.

Keywords Natriuretic peptide · Cyclic guanosine monophosphate (cGMP) · Neprilysin · Neutral endopeptidase · Heart failure · Preclinical

Introduction

The mainstay of the current guideline recommended heart failure (HF) therapy is neurohumoral inhibition including beta-receptor blockers and inhibitors of the renin-angiotensin-aldosterone system (RAAS) [1, 2]. Despite these effective neurohumoral inhibitors, the prevalence and burden of HF continues to rise [3–5]. This is not for lack of effort on behalf of the scientific community which has devoted immense resources and effort to the development of HF therapeutics but which unfortunately has resulted in no new novel therapies and little impact on long-term prognosis [6]. It has now been over a decade since the last HF pharmacologic therapy was approved and there is a clear unmet need for novel therapeutics. The lack of progress in the HF arena is in part related to the multitude of etiologies leading to HF. HF is the final common phenotype for various pathophysiologic mechanisms ranging from ischemic heart disease to rare genetic anomalies to age-related cardiac remodeling and diastolic dysfunction. A key challenge in the HF community is therefore to develop novel therapeutics which can be applied to the appropriate patient at the ideal time. One such potential therapeutic target is the natriuretic peptide system (NPS). The NPS is intimately involved in cardiorenal homeostasis in health, and dysregulation of the NPS plays an important role in the pathophysiology of HF. Chronic augmentation of the protective NPS and activation of the endogenous particulate guanlylyl cyclase (GC)/cyclic guanosine monophosphate (cGMP) pathway in the early stages of HF may ultimately prevent the progression of HF and reduce subsequent morbidity and mortality. In the current manuscript, we review the rationale for as well as previous and current efforts aimed at chronic therapeutic augmentation of the NPS in HF.

An Overview of the Natriuretic Peptide System

The first report of a NP produced in the heart appeared more than 30 years ago when researchers in Canada and Japan reported almost simultaneously reported the gene for atrial natriuretic peptide (ANP) [7, 8]. We now know the NP family consists of three structurally similar although genetically and physiologically distinct peptides: ANP, B-type (or brain) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). All three play an important role in cardiorenal homeostasis and possess cardiorenal protective properties particularly in cardiovascular disease.

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Both ANP and BNP are produced in the cardiomyocyte as preprohormones. Traditionally, it was thought that ANP is secreted into circulation as biologically active $ANP_{1–28}$. However, recent data suggest $proANP_{1–126}$ is also secreted into circulation where it has distinct biologic actions in addition to undergoing cleavage to $ANP_{1–28}$ [9]. BNP is secreted into circulation as $BNP_{1–108}$ which possesses limited biologic actions and then cleaved by corin or furin into potently biologically active $BNP_{1–32}$ and biologically inactive NT-proBNP [10]. ANP and BNP preferentially bind the GC-A receptor and activate the second messenger molecule cGMP. Binding to GC-A and activation of cGMP results in diuresis/natriuresis, vasorelaxation, inhibition of the RAAS, inhibition of vascular/renal/cardiac fibrosis, and positive lusitropy [11, 12•, 13, 14].

CNP differs from ANP and BNP as it is preferentially produced in the endothelial cell and binds preferentially to the GC-B receptor [15, 16]. While both GC-A and GC-B activate cGMP, they are differentially expressed thereby resulting in markedly distinct biologic actions. CNP is a venodilator and has more potent antifibrotic actions compared to ANP and BNP but lacks renal actions [17–19].

All three NPs are cleared from the circulation by the NP receptor C (NPR-C) which is not cGMP-linked although it has been shown to have anti-proliferative properties, particularly related to CNP binding [20, 21]. All three peptides also undergo proteolytic degradation by the ectoenzyme neutral endopeptidase 24.11 (NEP) which is also known as neprilysin and the zinc metalloprotease insulin-degrading enzyme (IDE) [12•, 22–24]. NEP is most abundant in the kidney but is widely expressed [25–27]. NEP cleaves the ring structure of ANP, BNP, and CNP thereby rendering the peptides unable to bind to GC-A and GC-B and therefore essentially inactive [28–30]. Importantly, the C-terminus tail of the NP is important in providing resistance to NEP degradation. Thus, CNP which has no C-terminus is rapidly degraded when compared to ANP or BNP and in particularly to chimeric peptides such as CD-NP (cenderitide) or M-ANP [28, 30–32] which have elongated C-terminus tails. ANP is the preferred substrate for IDE versus BNP and CNP. There is also exciting data suggesting the IDE cleavage may modulate the GC-A and GC-B response to the NPs. Specifically, BNP induced GC-A activation is enhanced by IDE (and decreased by IDE inhibition) suggesting that IDE cleavage of BNP results in a variant which is a super GC-A activator [23, 25]. In contrast, IDE inhibition increases GC-A and GC-B activation by ANP and CNP respectively.

Heart Failure: a Natriuretic Peptide Deficiency State

Following the seminal discovery of ANP, numerous studies quickly established that ANP and BNP levels are markedly elevated in the HF patient and have subsequently played an important role in the diagnosis and risk stratification in HF [33–39]. The activation of the NPS initially serves as a counter mechanism to the profound humoral and inflammatory milieu of HF. However, it is now clear that activation of fetal gene pathways and altered proteolysis renders the vast majority of measured ANP and BNP in HF patients biologically inactive. Therefore, these patients do not benefit from the pleiotropic anti-proliferative, cardiac unloading, and RAAS-inhibiting properties of biologically active $ANP_{1–28}$ and $BNP_{1–32}$. Based on the phenomena of high measured NP levels with little biologic activity, we and others have therefore proposed that HF is a relative NPS deficient state.

High-sensitive mass spectrometry data supports the concept of a relative NPS deficiency state in HF. Hawkridge et al. [40] demonstrated an absence of $BNP_{1–32}$ from the plasma of patients with NYHA class IV HF. Furthermore, Niederkofler and colleagues compared a point-of-care BNP assay with mass spectrometry and found that the point of care assay grossly overestimates the amount of biologically active $BNP_{1–32}$ [41]. Additional studies suggest the majority of measured BNP among HF patients is proBNP [42, 43] or altered BNP molecular forms including 3–32, 4–32, 5–32, 5–31, 1–25, and 1-26 [44–47]. Importantly, these altered BNP molecular forms less potently activate GC-A than $BNP_{1–32}$ [48, 49] and do not result in the same beneficial cardiorenal effects. The exact mechanism of the predominance of the altered BNP forms remains to be elucidated but is in part secondary to abnormal glycosylation [50, 51] and processing within the myocyte and in the plasma [45, 52]. Studies suggest corin and dipeptidyl peptidase IV (DPP4) may also play a role in the abnormal NP processing in HF. DPP4 converts $BNP_{1–32}$ to $BNP_{3–32}$ and inhibition of DDP4 results in improved cardiorenal function in experimental HF [53]. Over expression of corin which cleaves proANP and proBNP to the active molecular forms is associated with improved cardiac function in an animal model of HF [54]. Importantly, a preponderance of these altered molecular forms may explain the paradox of elevated NP levels in HF without the associated beneficial cellular and hemodynamic actions. This paradox also explains the acute response to exogenous NP administration despite elevated NP levels in HF.

Beyond overt HF, in both preclinical (stage B) systolic and diastolic HF we have demonstrated an impairment of the NPS particularly in response to intravascular volume expansion (i.e., a fluid challenge). Specifically, there is an inappropriate diuretic and natriuretic response to volume expansion which is associated with impaired activation of urinary cGMP. This finding suggests there is impairment of the NPS in the early stages of HF which results in altered volume handling. It is tempting to speculate that NPS impairment which negatively impacts volume handling in preclinical HF may play a role in the development and progression of symptomatic HF.

Importantly and with therapeutic implications, this NPS impairment in stage B HF was overcome by a single dose of exogenous BNP [55].

Exogenous Supplementation of the NP System

The pleiotropic beneficial cellular and cardiorenal actions of the NPS make therapeutic augmentation an attractive pharmacologic target in HF. Indeed, exogenous intravenous BNP (nesiritide) and ANP (carperitide) are approved for the treatment of acute decompensated HF in the USA and Japan, respectively. Nesiritide was approved in 2001 based on studies which demonstrated a reduction in cardiac filling pressures and improvement in dyspnea [56, 57]. However, a subsequent meta-analysis of multiple small studies raised concern about adverse renal effects and increased mortality associated with nesiritide use [58, 59]. These concerns were the impetus for the large ASCEND-HF study [60] with over 7000 participants which compared a 72-h intravenous nesiritide infusion to standard of care in acute decompensated HF. ASCEND-HF demonstrated no increase in mortality or adverse renal effects with nesiritide compared to standard of care. There was a small but statistically significant improvement in dyspnea with nesiritide. However, nesiritide did not improve mortality or hospital readmission rates. Based on these results and the recent ROSE study [61], the routine use of intravenous nesiritide in the acute decompensated HF patient is not guideline-recommended [62]. Intravenous carperitide continues to be used in the treatment of acute decompensated HF in Japan. While no large clinical trials on the order ASCEND-HF have been completed with carperitide, smaller studies suggest improvement in functional class during hospitalization and improvement in mortality without adverse renal effects [63, 64]. Some authors have postulated carperitide compares favorably to nesiritide in that it has a short half-life, does not mandate a bolus infusion which is associated with hypotension and adverse renal effects, and is used as a single agent (not as an addition to conventional diuretic therapy) [64]. Nonetheless, large randomized clinical trials are needed to make more definitive recommendations on the routine use of carperitide in HF.

We and others have suggested that many of the beneficial cardiorenal effects of the NPS in HF such as neurohumoral inhibition, cardiac unloading, and antifibrosis may not be fully optimized after 72 h of therapy as was performed in ASCEND-HF. The same could be argued for ACE inhibitors and beta-blockers. Therefore, we have hypothesized that chronic NP administration will improve HF outcomes where acute administration was not effective. Chen and colleagues tested this hypothesis in symptomatic HF in the NICE study [65•]. Patients with advanced (stage C) systolic HF were given either subcutaneous (SQ) BNP (10 μg/kg) twice daily or placebo in addition to standard of care for 8 weeks. SQ BNP was associated with improved left ventricular remodeling and filling pressures, improved functional class, and greater RAAS suppression than standard of care alone. Importantly, SQ BNP was not associated with an adverse effect on renal function. We have further assessed 12 weeks of SQ BNP therapy compared to placebo in asymptomatic (stage B) systolic HF [66]. Our results suggest BNP is associated with improved LV remodeling in stage B systolic HF. Further, the cardiorenal response to volume expansion is improved with chronic SQ BNP compared to placebo. Importantly, chronic SQ BNP in stage B HF did not adversely affect renal function. Chronic therapy may represent a new paradigm for exogenous NP therapy [67], and these proof-of-concept studies in stage B and C HF raise the specter that low dose, chronic exogenous NP therapy may capitalize on the pleiotropic beneficial cardiorenal actions of the NPS. Larger studies are planned and clearly needed for more definitive conclusions.

A potential drawback to peptide versus small-molecule therapeutics is the delivery mechanism as oral peptide administration is not currently cost effective [68]. Subcutaneous administration is currently the most effective delivery mechanism, and exciting advances are underway with the advent of pump-and-patch delivery systems. While the lack of an efficient oral delivery mechanism is a potential drawback, there are significant physiologic advantages to peptide therapy. Specifically, peptide therapeutics are highly specific for their receptors without significant cross reactivity which is common with small molecules.

NEP Inhibition

Beyond exogenous NP administration, inhibition of biologically active peptide degradation has significant therapeutic potential. As reviewed above, the NPs are removed from circulation via enzymatic degradation and the clearance receptor NPR-C. There are currently no therapeutic NPR-C inhibitors. Of the inhibitors of enzymatic NP degradation, the most clinically advanced are the NEP inhibitors. In experimental HF, candoxatril, an orally available small molecule NEP inhibitor, increased NP levels, promoted natriuresis/diuresis, and decreased aldosterone levels [69]. Candoxatrilat, an intravenous NEP inhibitor, increased NP levels and promoted diuresis in experimental mild HF but not in severe HF [70]. Candoxatril and candoxatrilat results in human HF were mixed. Small human studies with candoxatril demonstrated it was well tolerated and increased exercise tolerance and improvement in HF symptoms [71–73]. However, other human studies demonstrated systemic vasoconstriction and decreased cardiac index in HF [74, 75]. Ecadotril, another NEP inhibitor, was found to have limited beneficial effects on functional

capacity and was associated with an increased risk of aplastic anemia in a small HF study [76].

It is important to note that in addition to promoting degradation of NPs, NEP also is involved in the degradation pathways of endothelin, angiotensin, and calcitonin gene-related peptide [77]. Specifically, NEP inhibition increases circulating plasma levels of endothelin and calcitonin gene-related peptide which may counteract the beneficial actions of increased NP levels [75]. NEP inhibition also impairs the degradation of ANG-1 to ANG-(1–7). ANG-(1–7) has been described as a potent diuretic and natriuretic agent [78–80]. It increases renal blood flow [81] and produces afferent arteriolar relaxation through specific receptor-mediated nitric oxide release [82] in animal models. The increase in ET-1 and calcitonin gene-related peptide as well as reduced ANG-(1–7) may counter the beneficial cardiorenal effects of isolated NEP inhibition. Due to increased levels of vasoactive peptides and a lack of consistently beneficial clinical effects among HF cohorts, the clinical development of isolated NEP inhibitors was discontinued in favor of dual ACE/NEP inhibitors.

Combination ACE and NEP Inhibitors

The combination of NEP and ACE inhibitors was hypothesized to limit the detrimental effects of increased angiotensin II associated with isolated NEP inhibition thereby maximizing the benefit of increased NP levels. This novel therapeutic class consists of single-molecule inhibitors of both ACE and NEP and is commonly referred to vasopeptidase inhibitors (VPIs). Well-studied examples include sampatrilat and omapatrilat. Sampatrilat is a potent inhibitor of both ACE and NEP with attractive humoral and hemodynamic properties in HF [83]. However, the clinical development was discontinued due to poor oral bioavailability [84] and relatively weak ACE inhibition [85]. Omapatrilat, which has good oral bioavailability, is the most studied VPI. Omapatrilat has equal affinity for NEP and ACE and is an avid inhibitor of both [86, 87]. In animal HF models, it improved cardiac dysfunction and promoted beneficial remodeling [88, 89]. Early studies with omapatrilat in human HF were positive. In the prospective, doubled-blinded IMPRESS study which compared omapatrilat to lisinopril in 573 HF subjects, there were improvements in the combined endpoint of death, hospitalization, or discontinuation of study treatment due to worsening HF with omapatrilat versus lisinopril [90]. The much larger OVERTURE study [91] where 5770 participants were randomized to either omapatrilat (40 mg daily) or enalapril (10 mg twice daily) demonstrated that omapatrilat reduced the risk of death and rehospitalization in HF. However, omapatrilat was not more effective than enalapril alone.

It is important to note that in the very large OCTAVE study, which compared omapatrilat to enalapril in over 25,000 hypertensive subjects, significantly higher prevalence of angioedema with omapatrilat versus enalapril was demonstrated (2.2 versus 0.7 respectively) [92]. In the OVERTURE study, the incidence of angioedema with omapatrilat was 0.8 versus 0.5 % with enalapril. The increased incidence of angioedema with combination ACE and NEP inhibitors, particularly with omapatrilat, is thought to be secondary to increased levels of bradykinin [87] in a similar fashion to ACE inhibitors. However, aminopeptidase P (APP) which plays an important role in bradykinin degradation and is avidly inhibited by omapatrilat may play a role in greater incidence of angioedema when compared to ACE inhibition alone. Omapatrilat significantly inhibits APP more so than sampatrilat, and it has been suggested that the increased angioedema observed in the OCTAVE study was specific to omapatrilat and not a class effect of the VPIs [93, 94]. Based primarily on safety concerns, the FDA has not approved omapatrilat for clinical use and therapeutic investigation moved to combination angiotensin receptor blockers (ARBs) and NEP inhibitors.

Combination ARB and NEP Inhibitors

The incidence of angioedema is markedly lower with angiotensin receptor blockers (ARBs) compared to ACE inhibitors, and it was hypothesized that a combined AT-1 and NEP inhibitor would have the same beneficial properties as combined ACE/NEP inhibition without the adverse angioedema effects. The combination ARB and NEP inhibitor are commonly referred to as ARNi (angiotensin receptor neprilysin inhibitors) compounds. By far, the most advanced clinically developed ARNi is LCZ 696 [95]. LCZ 696 is a combination of the NEP inhibitor prodrug AHU-377 which is converted to active metabolite LBQ 657 and valsartan in a 1:1 ratio. In preclinical studies, LCZ 696 reduced blood pressure and increased cGMP levels [96]. In human hypertensive disease, LCZ 696 was more effective at lowering blood pressure than valsartan alone and there were no cases of angioedema [97•]. The PARADIGM-HF study [98•] was designed to assess the efficacy and safety of LCZ 696 in the setting of systolic HF in over 8000 patients so as to provide robust data on the potential benefit of augmentation of the NP system in combination with a specific AT1 blocker and concomitant standard medical therapy. The primary endpoint is combined cardiovascular death and HF readmission although the study was powered to demonstrate a 15 % relative reduction in cardiovascular death. In March 2014 the Data Monitoring Committee unanimously recommended early closure of the PARADIGM-HF trial as the primary endpoint was met although results are not currently available. This development is highly encouraging that after decades of intense research, an effective therapeutic aimed at chronic augmentation of the NPS in HF may be soon

available. If approved, this will be the first new pharmacologic therapeutic class for the treatment of HF in over 15 years.

Another interesting development in the LCZ 696 story is the recently published PARAMOUNT trial [99•] which was a phase II study which assessed LCZ 696 in the setting of HF with preserved ejection fraction (HFpEF) where effective treatments are severely lacking. In HFpEF, LCZ 696 was well tolerated and associated with a significant reduction in plasma NT-proBNP compared to valsartan alone. However, it is not known if this reduction in NT-proBNP translates into improved clinical outcomes. Larger studies of LCZ 696 in HFpEF are planned and are essential before a recommendation regarding LCZ 696 can be made in HFpEF.

A Focus on Heart Failure Prevention

Beyond symptomatic systolic HF, there is tremendous potential for chronic therapeutic augmentation of the NPS in early stages of HF. As noted above, we have demonstrated there is impairment of the NPS in stage B systolic HF which may play a role in the progression to symptomatic (stage C) HF. Future studies are needed to assess if combined ARB/NEP inhibition is able to slow or prevent the progression from stage B to C HF. In addition, many of the risk factors for HF are associated with abnormalities in the NPS. Specifically, ANP plays an important role in blood pressure regulation and a genetic polymorphism (rs5068) associated with higher levels of ANP is associated with a lower risk of hypertension [100]. A study from Olmsted County, Minnesota, demonstrates this same ANP gene polymorphism (rs5068) associated with higher levels of ANP is protective against obesity and syndrome [101]. It is tempting to think that early chronic augmentation of the NPS in these high-risk cohorts (i.e., stage A HF) before the onset of structural changes may ultimately prevent HF. Indeed, we would hypothesize that non-hypotensive augmentation of the NPS may prevent adverse cardiac, renal, and vascular remodeling which are remarkably difficult to reverse once present. These areas clearly need to be explored and may have significant impact on cardiovascular morbidity and mortality.

Future Directions

The clinical development of therapeutic augmentation of the NPS continues to advance on multiple fronts. Small molecule augmentation of the NPS via the ARNi compound LCZ 696 is moving forward at great speed. Exogenous NP therapeutics continue to advance with the development of chimeric NPs which possess enhanced properties and/or pharmacokinetics as compared to native NPs [32, 102–106]. These designer peptides possess refined affinity for the GC-A and GC-B receptors which translate into more biological actions specific for various cardiovascular disease subsets. These designer peptides are also resistant to enzymatic degradation allowing for once-daily administration [32, 107]. The delivery mechanisms for NP therapeutics continue to advance beyond simple single use SQ therapy with the increasing use of pump and patch delivery systems and developing oral delivery technologies [108]. We anticipate future studies of exogenous peptide administration and the ARNi compounds in stage B HF as well as hypertension and metabolic syndrome with the ultimate goal of preventing HF.

Summary and Conclusion

The NPS is recognized to play a fundamental role in cardiorenal homeostasis promoting diuresis, vasorelaxation, beneficial remodeling, and potent neurohumoral inhibition. These actions support the development of chronic augmentation of the NPS for HF. Indeed, a HF therapeutic which lowers LV filling pressures, inhibits the RAAS, promotes diuresis/natriuresis, enhances renal function, and promotes beneficial remodeling is highly attractive. The results of the large PARADIGM-HF trial [98•] will provide important specific data on HF outcomes associated with NPS augmentation via NEP inhibition. We anticipate the PARADIGM-HF trial will trigger FDA approval and the subsequent clinical use of NEP inhibition in HF. This is highly anticipated data particularly in an era of persistently poor HF outcomes and a lack of novel pharmacologic therapeutics over the last two decades.

Compliance with Ethics Guidelines

Conflict of Interest Paul M. McKie declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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