The natriuretic peptide system (NPS) provides critical compensatory actions in heart failure, including vasodilation, promoting of natriuresis; and opposing adverse neurohormonal activation, including the renin-angiotensin-aldosterone axis. The NPS also is an autocrine/paracrine neurohormonal system that enhances lisitropy, opposes cardiac hypertrophy, and retards the development of cardiac neurohormonal activation, including the renin-angiotensin-aldosterone axis. The NPS also is an autocrine/paracrine neurohormonal system that enhances lusitropy, opposes cardiac hypertrophy, and retards the development of cardiac neurohormonal activation, including the renin-angiotensin-aldosterone axis.

The hypotheses offered to explain the dysregulation of the NPS in heart failure focused on the NP receptor. The receptor mediating the target tissue actions of ANP and BNP is the guanylate-cyclase type A (GC-A) receptor. The binding of ANP or BNP to GC-A initiates a conformational change in the receptor that allows the intracellular guanylate-cyclase moiety of the receptor to effectively generate cGMP, the primary second messenger mediating downstream signaling cascades in target tissues (vascular endothelium, zona glomerulosa of the adrenal gland, cardiac myocytes, cardiac fibroblasts, and renal epithelial cells). The cGMP pool produced from GC-A activation has distinct signaling functions and is compartmentalized from the cGMP pool generated from soluble guanylate cyclase, which is activated by the nitric oxide signaling pathway. It is postulated that the specificity of plasma cGMP for GC-A activation relates to the proximity of the GC-A-derived cGMP pool to the cellular membrane that facilitates extracellular egress of this cGMP pool. Largely the result of seminal biochemical studies from Potter and colleagues, it is known that chronic ligand occupancy of the GC-A receptor leads to “homologous desensitization” of the GC-A receptor. At the molecular level, GC-A desensitization is the consequence of dephosphorylation of the kinase homology domain of GC-A, which blocks the conformational change in GC-A required to activate the guanylate-cyclase moiety. Thus, the data from Tsutomota and colleagues were largely attributed to GC-A desensitization that was presumably the result of chronic elevations of ANP and BNP in more advanced heart failure. In addition, postreceptor mechanisms were identified as contributing to the observed loss of the ability of ANP and BNP to exert their expected biological effects. For example, heart failure is associated with upregulation of phosphodiesterase 5, which degrades cGMP, and blockade of phosphodiesterase 5 augmented the hemodynamic response of exogenously administered BNP in a canine model of severe heart failure.

The efficacy of recombinant BNP₃₂ (nesiritide) as a therapeutic agent in patients with acute decompensated heart failure challenged the hypothesis that GC-A desensitization was the explanation for the “attenuated compensatory actions” of the NPS in advanced heart failure. The VMAC (Vasodilatation in the Management of Acute Chronic Heart Failure) study enrolled patients with acutely decompensated heart failure and reported that the administration of recombinant BNP₃₂ resulted in rapid and sustained improvements in hemodynamic parameters and reductions in adverse neurohormonal activation. The robust hemodynamic and neurohormonal responses to nesiritide suggest that the GC-A receptor is not significantly desensitized in advanced heart failure, suggesting that other mechanisms may account for the previously described observations from Tsutomota and colleagues. What other potential mechanisms exist?

Recent attention has focused on potential problems with the GC-A ligands in advanced heart failure. Similar to other peptide hormones, both ANP and BNP are produced as prohormones that undergo proteolytic cleavage into biologically active, 28- and 32-amino acid, carboxyl-terminal peptide hormones, respectively (Figures 2 and 3). The importance of adequate NP processing to the in vivo function of the NPS relates to the fact that NP processing is required for the prohormones to attain maximal capacity to activate GC-A. Two in vitro studies have clearly demonstrated that compared
to BNP$_{32}$, unprocessed BNP$_{1-108}$ has substantially reduced capacity to activate the GC-A receptor.$^{11,12}$

The available data suggest that the predominant enzyme responsible for NP processing (cleavage) is corin, a type II transmembrane serine protease, expressed predominantly in cardiomyocytes and first identified by Yan and colleagues.$^{13,14}$ Using in vitro cell culture systems, they demonstrated that corin was capable of processing proANP and proBNP in vitro. An analysis of the structure of corin reveals that the catalytic domain is located in the extracellular region of corin. The current hypothesis is that proANP and proBNP are secreted through exocytosis and processed on the cardiomyocyte surface. Corin may not be the only enzyme involved in NP processing; for example, in vitro studies have demonstrated that furin, an endopeptidase, is capable of processing BNP$_{1-108}$.$^{15}$

Recent studies have demonstrated that in advanced heart failure, a significant proportion of circulating BNP is unprocessed BNP$_{1-108}$.$^{16,17}$ The reason this was not immediately apparent, given the widespread use of BNP measurement as a prognostic and diagnostic biomarker, is the fact that the most commonly used immunoassays for BNP, such as the Biosite Triage assay, significantly cross-react with BNP$_{1-108}$. There has been some discrepancy between reports about the degree of cross-reactivity between BNP$_{1-108}$ and the commonly used Biosite BNP assay. This discrepancy likely is explained by the fact that one group used a glycosylated recombinant BNP$_{1-108}$, and the other group used a nonglycosylated form. In humans with heart failure, circulating BNP$_{1-108}$ is glycosylated and significantly cross-reacts with the Biosite BNP assay.$^{11,12}$ Therefore, it is not possible to accurately determine with these assays the proportion of BNP$_{32}$ and BNP$_{1-108}$ contributing to the measured BNP value in a given patient. However, when mass spectrometry was used to distinguish the molecular forms of BNP in humans with heart failure with substantially elevated BNP levels, measured with the Biosite assay, there was a surprising absence of BNP$_{32}$. Subsequently, a novel immunoassay has been developed that is specific for BNP$_{1-108}$ and demonstrates no significant cross-reactivity with either N-terminal (NT) BNP or BNP$_{32}$. With this assay, it was demonstrated that there is a positive correlation between BNP$_{32}$ and BNP$_{1-108}$ levels across a spectrum of heart failure severity, but the proportion of BNP$_{1-108}$ generally increases in parallel with the severity of heart failure. The adequacy of BNP processing appears to contain prognostic import. For example, a recent study from a longitudinal cohort of patients with moderate to severe heart failure demonstrated that the severity of impaired BNP processing is independently associated with increased risk for heart failure progression, need for transplant, and mortality.$^{18}$

In this issue of *Circulation: Heart Failure*, Ibebuogu and colleagues$^{19}$ relate the phenomenon of impaired NP processing to ANP for the first time in humans with acute decompensated heart failure. The authors examined the levels of processed and unprocessed ANP in 14 patients with severe...
heart failure compared to normal controls, using novel immunoassays specific for uncleaved proANP (authors terminology; in reality, ANP, 1-126), and cleaved ANP (the amino fragment NT-ANP). They report that in patients with advanced cardiomyopathy and acute decompensation, there is a significant increase in both cleaved and uncleaved proANP, consistent with impaired proANP processing. In addition, the authors examined the correlation of processed versus unprocessed ANP with plasma cGMP. This analysis revealed that cleaved NT-ANP was positively correlated with plasma cGMP levels, but there was no correlation between uncleaved proANP and plasma cGMP levels. This observation suggests that unprocessed ANP has reduced capacity to activate GC-A. Lastly, using a commercially available immunoassay for human corin, the authors demonstrated that acute decompensated heart failure is characterized by a substantial decrease in plasma corin levels compared with that of the control population. The intriguing question that emerges from these data relates to the potential significance of the reduced plasma corin levels to the pathophysiology leading to impaired ANP (and likely BNP) processing.

Focusing on corin as a nodal point of impaired NP processing makes an assumption about the importance of corin to NP processing. As previously mentioned, other enzymes, such as furin, may be involved in NP processing, but data suggest that corin may be most important to this process. For example, the corin knockout mouse develops salt-sensitive hypertension, an expected phenotype resulting from interruption of the NPS, and the analysis of circulating forms of ANP in the corin knockout mouse on a high-salt diet demonstrated the presence of unprocessed proANP alone; of note, data for plasma BNP processing was not reported by the investigators. The apparent absence of proANP processing in the corin knockout mouse suggests corin’s central importance (at least for proANP). Additional evidence of the centrality of corin to NP processing in vivo is derived from genetic epidemiological studies. In humans, a corin minor allele that is defined by the presence of the missense mutations (T555I and Q568P) in linkage disequilibrium is common in blacks and associated with increased risk for hypertension and cardiac hypertrophy. In vitro studies revealed that corin containing the 2 mutations has significantly reduced catalytic activity and processes proANP and proBNP less effectively. Moreover, in the A-HeFT (African-American Heart Failure Trial) study, the corin I555 (P568) allele was associated with greater severity of impaired BNP processing and an increased risk for heart failure progression in the absence of treatment with hydralazine-isosorbide dinitrate.

It is only recently that corin has been identified in plasma, and its significance is incompletely understood. As mentioned, the current paradigm of NP processing suggests that the primary site of NP processing is the cardiomyocyte surface where the prohormones interact with corin’s extracellular catalytic domain. The current study is not the first to report reduced plasma corin levels in heart failure. A previous study demonstrated that plasma corin levels were reduced in heart failure and reported that the reduction in plasma corin levels correlated with the severity of heart failure. It remains uncertain from these studies whether the corin detected in plasma possesses intrinsic biological activity. No splice variants producing a soluble form of corin have been identified to date. The corin protein being measured using this commercially available corin assay has not been isolated, purified, and molecularly characterized. There is, however, a recent study that is the first to demonstrate that plasma is capable of ex vivo processing of BNP. These researchers report that when His-tagged BNP was added to fresh plasma or serum, the BNP was processed to a lower-molecular-weight form, and processing capacity of plasma was correlated with measured plasma corin levels. However, the significance of plasma-mediated NP processing in human heart failure, the importance of plasma corin to this process, and the source of the plasma corin remain imprecisely characterized at the present time.

Reductions in plasma corin might suggest corin protein deficiency in the myocardium. If so, perhaps cardiac corin levels are simply insufficient to maintain adequate efficiency in NP processing under the conditions of high NP release characteristic of advanced heart failure and periods of decompensation. However, this hypothesis is not consistent with existing data. In fact, nature seems to have anticipated the need to augment corin-mediated NP processing under conditions of enhanced NP production and secretion. For example, the corin promoter contains many of the same transcription factor binding sites as the ANP and BNP promoters, including functional GATA4 elements. Consequently, corin and ANP and BNP gene expression would be predicted to be co-upregulated under conditions that activate the hypertrophic gene cascade, such as cardiac pressure and volume overload. Consistent with this, animal models of heart failure generally have demonstrated that corin mRNA levels increase in parallel with increases in ANP or BNP mRNA abundance.

More recent data suggest that the rate-limiting step in NP processing may be corin activation rather than corin abundance per se. Corin is a heavily glycosylated protein that is produced as an inactive zymogen requiring activation to gain biological activity. Activation of corin involves a specific proteolytic cleavage at amino acid position 801, just proximal to the catalytic domain. The proteolytic cleavage that activates corin results in the catalytic domain of corin remaining attached to the membrane-anchored corin molecule by disulfide bonds between adjacent cysteine molecules. The specific mechanisms of corin activation are still a mystery. An exciting recent study examined corin protein levels and corin catalytic activity using a novel fluorescent substrate proANP processing assay in the left ventricles from human hearts with end-stage cardiomyopathy obtained at the time of cardiac transplant. The authors demonstrated that in contrast to plasma corin levels, corin protein levels are significantly increased in the left ventricles of patients with advanced heart failure. Despite the increase in corin protein abundance, corin catalytic activity was not increased. Based on the increase in corin protein levels, with no corresponding increase in catalytic activity, the authors suggested that corin activation is impaired in heart failure and that this may be the essential rate-limiting step to NP processing. Perhaps plasma
corin, now demonstrated to be reduced in 2 independent studies, correlates with activated corin protein in the heart.

In conclusion, there are many more questions than answers emerging from recent studies of the NPS in heart failure. Indeed, it is an exciting time for researchers involved in NP biology. Although effective pharmacological approaches in heart failure have focused on opposing activation of adverse neurohormonal systems, researchers are focusing on ways to augment compensatory actions of the endogenous NPS as an alternative and complementary approach. The discovery that impaired NP processing is common in heart failure suggests a target, but translation to the bedside will require answers to the myriad emerging questions from recent research. The present study from Ibebuogu and colleagues certainly adds to the general excitement of this research enterprise and identifies many areas for future research.

Disclosures

None.

References

Process Matters: Emerging Concepts Underlying Impaired Natriuretic Peptide System Function in Heart Failure

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