The focus on brain natriuretic peptide (BNP) as a biomarker, the elevation of which is associated with adverse outcomes in persons with heart failure, has obscured recognition of the myriad beneficial and compensatory biological actions provided by this small peptide hormone. Both atrial and ventricular cardiomyocytes synthesize and release both atrial natriuretic peptide (ANP) and BNP in response to volume or pressure overload, most specifically, an increase in myocardial transmural distending pressure. These peptide hormones activate the natriuretic peptide receptor type A, which contains a guanylate–cyclose domain, and this leads to the production of cGMP and the activation of downstream signaling cascades. The resulting biological actions in target tissue include the following actions that are universally beneficial in the setting of hypertension, hypertensive heart disease, and heart failure: venous and arterial vasodilation, maintenance of appropriate intravascular volume by promoting natriuresis, opposing activation of the renin–angiotensin–aldosterone system, reduced secretion of endothelin, and attenuation of central and peripheral sympathetic activity.1

BNP is produced as prohormone that undergoes further processing (Figure). After removal of the 26 amino acid signal peptide from the pro-BNP molecule, pro-BNP (1-108) is secreted from cardiomyocytes and interacts with an enzyme called corin, a transmembrane serine protease produced in cardiomyocytes, resulting in the production of a 76 amino acid amino terminal fragment (NT-BNP 1-76) and the biologically active 32 amino acid carboxyl fragment (BNP 77-108 or BNP-32).2 It is believed that the site of natriuretic peptide processing is the extracellular region of cardiomyocytes and possibly cardiac fibroblasts. Although corin appears to be unique in this capacity, other yet undiscovered enzymes may contribute to natriuretic peptide processing.

The compensatory biological actions of the NPS become attenuated in the setting of systolic heart failure, and it appears that the degree of reduced compensatory actions parallels the severity of heart failure.4,5 The biological basis for the reduced compensatory actions of the NPS is multifactorial: homologous desensitization of the natriuretic peptide receptor type A; downregulation of natriuretic peptide receptor type A in target tissue; upregulation of phosphodiesterases, including phosphodiesterase 5, leading to enhanced cGMP degradation; and augmented neutral endopeptidase activity.1 An intriguing hypothesis states that impaired natriuretic peptide processing may contribute to the amelioration of the in vivo compensatory actions of the NPS in the setting of systolic heart failure. For example, a recent study6 that used Fourier transform ion cyclotron resonance mass spectrometry reported the absence of mature BNP-32 despite markedly elevated levels of BNP measured by the Biosite assay. However, incompletely characterized high-molecular forms of BNP were observed. These data raised speculation that the Biosite assay may not be measuring what we thought it was and fueled speculation that, in certain clinical settings, such as advanced heart failure, natriuretic peptide processing may be inefficient and incomplete.

In this issue of Hypertension,7 Heublein et al demonstrate the cross-reactivity of various molecular forms of human BNP with commonly used commercial bioassays for BNP. The data demonstrate that the Biosite and Shionogi assays detect the biologically active forms of BNP (BNP 1-32 or 3-32) but do not measure NT-BNP (1-76) or unprocessed BNP (1-108). In contrast, the Roche NT-BNP assay measures NT-BNP (1-76), does not cross react with mature BNP1-32 or BNP3-32, but does demonstrate significant cross-reactivity with unprocessed BNP 1-108. The second significant finding reported by Heublein et al7 is the demonstration that unprocessed BNP (1-108) is biologically inactive, as illustrated by its inability to increase cGMP production in cardiomyocytes. Presumably, despite the fact that pro-BNP (1-108) possesses the disulfide ring required for biological activity of the natriuretic peptides, the tertiary structure of the larger BNP 1-108 molecule or resulting oligomerization prevents it from interacting effectively with the natriuretic peptide receptor type A receptor’s ligand binding domain. The lack of biological activity of unprocessed BNP (1-108) has not been demonstrated previously. However, the importance of adequate natriuretic peptide processing to the adequate function of the NPS was inferred by the observation that the corin knockout mice develop hypertension in the setting of circulating unprocessed ANP.8 Interestingly, the administration of a recombinant form of soluble corin to the corin knockout mice resulted in rapid appearance of processed ANP in the plasma, a parallel increase in plasma cGMP, and an immediate decrease in systemic blood pressure.
BNP Processing

preproBNP (134 aa)

proBNP (108 aa)

signal peptide (26 aa)

secretion

myocyte

Corin interaction

NT-BNP (aa 1-76)

BNP-32 (aa 77-108)

BNP processing. BNP is produced as a prohormone that is processed into its biologically active, carboxy-terminal fragment. The critical processing step occurs on the extracellular surface of cardiomyocytes when it interacts with corin, a type II transmembrane serine protease.

The data from Heublein et al. provide the rationale and a methodologic framework to explore the epidemiology, molecular basis, and prognostic import of impaired natriuretic peptide processing in various disease states. Such endeavors may lead to novel therapeutic and preventive strategies across the spectrum of hypertensive heart disease. In particular, the data reported by Heublein et al. demonstrate that 2 commonly used and validated bioassays (Biosite and Shiogoni) are specific for processed, biologically active BNP-32 and devoid of significant cross-reactivity with either NT-BNP (1-76) or pro-BNP (1-108). What is needed to address the research questions in this field is a specific assay for unprocessed pro-BNP (1-108). BioRad has reported the development of a specific bioassay for intact, unprocessed BNP 1-108 that should eventually be commercially available. The BioRad intact BNP assay uses a capture-antibody that reacts with epitopes in the “hinge region” (the region containing the cleavage site for corin) of the unprocessed BNP 1-108 molecule and a carboxy-terminal detection antibody. The simultaneous measurement of BNP using the Biosite (or Shiogoni) and BioRad intact BNP assays allows the simultaneous measurement of processed, biologically active BNP (1-32 or 3-32) and unprocessed, biologically inactive BNP (1-108).

There are intriguing questions that remain to be answered when considering the relationship of natriuretic peptide processing to the compensatory actions of the NPS in various disease states. One concept of potential relevance is that of “natriuretic peptide processing efficiency,” which an investigator might define as the ratio of circulating biologically active BNP (1-32 or 3-32) to unprocessed, biologically inactive BNP (1-108) or the percentage of biologically active BNP within the “total natriuretic peptide demand” BNP pool, defined as the sum total of biologically active BNP and unprocessed pro-BNP. Perhaps these concepts, when considered in the context of the well-elucidated biology of the NPS, might provide additional prognostic information in patients with heart failure and possibly identify patients who might benefit most from exogenous natriuretic peptide therapy. Although elevated levels of BNP are consistently associated with adverse outcomes in heart failure populations of mixed severity, a recent report within a relatively small but homogeneous population of patients with advanced heart failure demonstrated that nonsurvivors compared with survivors had lower BNP levels (Biosite). Could it be that a subpopulation of persons with advanced heart failure and a low Biosite BNP level might actually be in a “BNP deficient” state? A BNP deficient state might not be appreciated by measuring only biologically active BNP but rather by comparing the amount of biologically active BNP as a percentage of the “total natriuretic peptide demand.”

The demonstration of unprocessed BNP (1-108) in advanced human heart failure leads to speculation that there may be a deficiency in natriuretic peptide processing in this setting, and this may contribute to disease progression by ameliorating the compensatory actions of the NPS. Corin appears to be unique in its capacity as the “pro-ANP/BNP convertase”; therefore, the natriuretic processing capacity of corin may be overwhelmed when the transcription of ANP and BNP is excessive. Is the corin gene upregulated in heart failure to help maintain natriuretic peptide processing efficiency? A priori considerations would lead one to predict a parallel increase in corin, ANP, and BNP transcription based on an inspection of their promoter regions; the human corin, ANP, and BNP genes contain similar transcriptional factor binding sites, including functional GATA-4 binding domains. However, the 2 studies of corin expression in animal models of heart failure report conflicting results, with 1 reporting an increase and the other a decrease in corin expression. In a related human study that examined the correlation of corin and BNP gene expression in human hearts obtained at the time of heart transplant, an unexpected inverse relationship was observed; corin gene expression declined as BNP gene expression increased, perhaps providing the molecular background for impaired natriuretic peptide processing. Recently, a minor allele in the human corin gene, defined by 2 nonconservative, nonsynonymous polymorphisms in complete linkage disequilibrium, was demonstrated to be common in persons of African descent, associated with higher blood pressure, an increased risk for hypertension, and an enhanced cardiac hypertrophic response to pressure overload. The yet-unproven hypothesis underlying the association of the corin I555 (P568) allele with these phenotypes is that natriuretic peptide processing is impaired in the presence of the minor corin allele.

A better understanding of the physiology of natriuretic peptide processing will be an important area for future research with the field of natriuretic peptide physiology. The present data from Heublein et al., demonstrating the immunoreactivity and bioactivity of various molecular forms of BNP, provide the rationale and a methodologic approach to continue these research efforts. The data have the potential to yield important insights that may also improve preventive and treatment strategies in hypertension, the cardiac response to hypertension, and established heart failure.
Disclosures
None.

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Relevance of Molecular Forms of Brain Natriuretic Peptide for Natriuretic Peptide Research
Daniel L. Dries

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