It has been more than 2 decades since the seminal report by DeBold demonstrating the existence of atrial natriuretic peptide (ANP) as a cardiac hormone that links the heart and kidney in cardiorenal homeostasis. Since that discovery, a family of structurally similar but genetically distinct peptides have been reported that function via well-characterized particulate guanylyl cyclase receptors linked to cGMP. These include ANP and B-type natriuretic peptide (BNP), which are ligands for the natriuretic peptide receptor A, and C-type natriuretic peptide, which binds to the natriuretic peptide receptor B.

In the current issue, Rame et al focus attention on the processing of the cardiac peptide prohormones to mature biologically active peptides by the propeptide corin. This study was predicated by the work by Yan et al, which established corin as the natriuretic peptide-converting enzyme for ANP and presumably BNP (Figure). This cleavage of the prohormone to the mature peptide is essential for biological activity exemplified by a novel murine model of corin deletion in which the phenotype is hypertension and cardiac hypertrophy.

The work of Rame et al associating a corin polymorphism with ventricular hypertrophy in blacks builds on evidence of the importance of the natriuretic peptides as modulators of ventricular structure. Such genetic evidence of a link between the natriuretic peptides and myocardial structure is not surprising. Genetic mouse models in which either ANP or BNP or the natriuretic peptide receptor A have been deleted are characterized by cardiac hypertrophy and fibrosis independent of increases in arterial pressure. Such phenotypes are consistent with reports that the natriuretic peptides inhibit cardiomyocyte hypertrophy and cardiac fibroblast proliferation and collagen synthesis. Most recently, Rubattu et al reported in a study of 203 hypertensive subjects that those carrying an allelic variant in the ANP gene promoter had increased left ventricular mass incidence as compared with the wild-type genotype. These associations were independent from clinical factors and were confirmed in a subgroup of never-treated hypertensive subjects. Consistent with a biological effect on ANP production, carriers of the ANP gene promoter allelic variant had lower plasma pro-ANP levels. These investigators also observed that an natriuretic peptide receptor A receptor polymorphism was associated with myocardial structural changes in hypertensive subjects beyond that observed in hypertensive subjects without the genetic defect.

The current report by Rame et al further advances the concept of an autocrine and paracrine role for the natriuretic peptides in regulating cardiac structure. In this association study, the investigators identified a relationship between systolic blood pressure (SBP) and indexed left-ventricular mass in blacks from the stratified by corin allele status. The Multi-Ethnic Study of Atherosclerosis was used as a validation cohort. The focus on corin was based on their previous report that a minor allele in the corin gene defined by 2 highly linked single nucleotide polymorphisms (T5551 and Q568P) was associated with hypertension in blacks. They now have extended this report in the current issue of Hypertension observing that, in adjusted analysis in the Dallas Heart Study, the corin I555 allele was an independent predictor of left ventricular mass in subjects with elevated SBP. A significant nonlinear interaction between the corin I555 allele and SBP on indexed left ventricular mass was confirmed in the Multi-Ethnic Study of Atherosclerosis. They conclude that this minor corin I555 allele is associated with modification of the SBP–left ventricle relationship identifying individuals with an increased indexed left ventricular mass in the higher ranges of SBP. These data support the concept that the corin I555 allele is associated with an enhanced cardiac hypertrophic response to pressure overload in blacks being an example of a potential “LVH sensitizing” gene variant.

There are several questions that remain to be addressed to understand the clinical significance and biological mechanisms by which these observations by Rame et al link the natriuretic peptide system and myocardial structure, especially in hypertension. A demonstration in an animal model that this polymorphism can be translated into a phenotype of cardiac hypertrophy and/or fibrosis with or without hypertension would be helpful. The use of specific ANP and BNP assays to document accumulation of pro-BNP or pro-ANP with reduced biologically mature BNP or ANP would also go a long way to demonstrate that the genetic variant in corin results in reduced processing of a pronatriuretic peptide to the biologically active hormone. It should be noted, as stated by the authors, that a more comprehensive examination of the total allelic variation of the corin locus using a haplotype-based approach could yield additional insights and that a haplotype-based analysis of the corin locus is now feasible thanks to the efforts of the International HapMap Project.
The current findings have significant relevance to cardiovascular diagnostics and therapeutics, should these observations be clinically validated. A heritable predisposition to defective natriuretic processing may be particularly important in heart failure, based on work by Langenickel et al.\textsuperscript{10} demonstrating downregulation of corin activity in a rodent model of myocardial dysfunction. From a diagnostic perspective it will be important to identify carriers of this polymorphism among at-risk subjects and populations and then determine the ratio of pro-ANP to biologically active mature ANP or BNP. If there is a derangement in processing inactive (ie, propeptide) into biologically active (ie, mature) peptides, then natriuretic peptide replacement therapy could be envisioned. Recent studies by Cataliotti et al.\textsuperscript{11} from our group with a novel conjugate of human BNP, making the peptide orally available, makes such a concept feasible and attractive. The work of Rame\textsuperscript{3} reflects a growing understanding of the physiological relevance of the natriuretic peptide system beyond cardiorenal regulation, underscoring its role in modulation of myocardial structure.

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