Editorial

News From the Heart Natriuretic System

Ines Armando, PhD

Renal and nonrenal mechanisms are involved in the long-term regulation of blood pressure that is dependent on a precise balance among humoral agents and vasoconstrictor and vasodilator hormones and other factors that act to increase or decrease renal sodium transport. These imply a complex interaction between natriuretic and antinatriuretic systems. The dysregulation of ion transport intrinsic and extrinsic to the kidney has been proposed to cause essential hypertension.

See Article by Salo et al

An important natriuretic system is that comprising the cardiac hormones, atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP), playing a critical role in the reduction of blood pressure and cardiac disorders with relevance to renal and cardiovascular homeostasis. ANP is synthesized and stored in the atrial granules as a prohormone with 126 amino acids, proANP. BNP is deglycosylated from a 108-amino acid prohormone, proBNP, and further processed into an amino terminal fragment, NT-proBNP1–76, and a biologically active peptide, BNP77–108 or BNP1–32. BNP is also produced by the cardiac fibroblast on which it exerts its antifibrotic action. Both ANF and BNP are synthesized in and continuously secreted from atrial cardiomyocytes under basal conditions.[1] Other groups, however, have reported that the cardiac ventricle rather than the cardiac atrium is the main source of plasma BNP in normal subjects and patients with congestive heart failure, whereas the reverse is true in the case of left ventricular hypertrophy without systolic dysfunction.[2] Mechanical stretch of atrial muscle increases the rate of peptide secretion. Expression and secretion of ANF and BNP are increased in various cardiovascular pathologies, and their levels in blood are used in the diagnosis and prognosis of cardiovascular disease. Binding ANP or BNP to guanylyl cyclase/natriuretic peptide receptor-a induces cyclic guanylyl monophosphate as second messenger in the target organs mediating natriuresis, water diuresis, increasing glomerular filtration rate, decreasing systemic sympathetic activity, plasma volume, cardiac output, and blood pressure; and curbing myocardial fibroblastogenesis and hypertrophy of cardiovascular muscle cells.

In this issue, a large and thorough GWAS by Salo et al[3] clarifies differences between ANP and BNP and provides new insights into their physiological role. Previous GWAS have only studied BNP and NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) circulating levels, but there are no GWAS reports on ANP. This study included midregional proANP in the evaluation of the impact of the genetic variants on natriuretic peptides or blood pressure. This GWAS (genome-wide association study) replicated previous findings in 2 loci near *NPPA-NPPB* (Natriuretic peptide precursor A-natriuretic peptide precursor B) and *GALNT4* (polypeptide N-acetylgalactosaminyltransferase 4) and found a novel association of a single nucleotide polymorphism (SNP) near *PPP3CC* (protein phosphatase 3 catalytic subunit gamma) with the BNP:NT-proBNP ratio. Probably, the most significant finding of this new study is that in contrast with what has been already published, a detailed study of the SNPs in the *NPPA-NPPB* region demonstrated that SNPs associated with increased levels of midregional proANP did not associate with increased levels of BNP or NT-proBNP, whereas the only SNP associated with both BNP and NT-proBNP did not associate with midregional proANP, indicating that the SNP effects are specific. The other significant finding is that SNPs associated with midregional proANP also negatively associated with blood pressure or hypertension, whereas none of the SNPs that correlated with BNP, NT-proBNP, or their ratio associated with blood pressure. An intriguing finding of this study is the association of *PPP3CC* with BNP:NT-proBNP. As the authors indicate, *PPP3CC* codes for a catalytic subunit of calcineurin that is involved in the regulation of cardiac hypertrophic signaling.

Interestingly, calcineurin is also involved in renal dopamine receptor signaling.[4] There is a clear interaction between dopamine receptors and ANP. The natriuretic response to ANP requires an intact renal dopamine system.[5] ANP and dopamine may have additive effects on sodium excretion, and dopamine and ANP synergistically inhibit NHE3 (Na(+)-H+ exchanger isoform 3)[6] and Na^+/K^+ ATPase activity that is abolished by a D1R (dopamine D1 receptor) antagonist. The response is mimicked by cGMP, the second messenger for ANP, and requires dopamine binding to the D1-like receptor. The results of this study suggest that there may be other levels of interaction between ANP and dopamine receptors.

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Disclosures

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From the School of Medicine and Health Sciences, George Washington University, DC.

Correspondence to Ines Armando, PhD, School of Medicine and Health Sciences, George Washington University, 2300 I St NW, Washington, DC. E-mail iarmando@gwu.edu

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