Cardiac Natriuretic Peptides
Gaining Further Insights Into Structure–Function Relationships*

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While the initial investigations on the physiological and pathophysiological functions of the cardiac natriuretic peptides (NP), atrial natriuretic peptide (ANP), also known as atrial natriuretic factor (ANF), and B-type natriuretic peptide (BNP), centered on their role in the maintenance of water and electrolyte balance and other determinants of extracellular blood volume and vascular tone, the NP field has reached unexpected realms, including inflammation, lipid metabolism, and behavior, all described in many thousands of publications accumulated in the scientific literature since the discovery of ANF in 1981 (1). Not less significant is the use of these hormones as therapeutic agents and as biomarkers of cardiac disease (2–4).

The plethora of biological actions of the cardiac NP stems from their interaction with the natriuretic peptide receptor type A (NPRA) cognate receptor resulting in the generation of 3′,5′-cyclic guanosine monophosphate (cGMP). In this manner, receptor-mediated signaling modulates the activity of cGMP-dependent phosphodiesterases, kinases, and ion channels, all of which are present in nearly all cell types. These broad targets confer the participation of NPs in a wide variety of complex biological, physiological, and sometimes unexpected processes (5). A very good example of that is presented in the article by McKie et al. (6) in this issue of the Journal. These investigators report the biological properties of a mutant ANP identified in association with a familial form of atrial fibrillation (7). The mutation in the NPPA gene results in a frameshift that translates into the production of an anomalous 40-amino acid hormone, which is 12 amino acids longer by carboxyl extension than the circulating native 28-amino acid hormone, which is 12 amino acids longer by carboxyl translation with a familial form of atrial fibrillation (7). The biological properties of a mutant ANP identified in association with a familial form of atrial fibrillation (7). The mutation in the NPPA gene results in a frameshift that translates into the production of an anomalous 40-amino acid hormone, which is 12 amino acids longer by carboxyl extension than the circulating native 28-amino acid hormone. McKie et al. (6) show that this results in enhanced natriuretic and diuretic effects and in an increased glomerular filtration rate, increased suppression of the renin-angiotensin-aldosterone system, and greater cardiac unloading and blood pressure-lowering properties when compared with native ANP. Albeit modest, these changes are statistically significant, and importantly, they suggest strategies to improve upon the biological potency or the half-life of the hormone for therapeutic purposes in cardiorenal disease. This is a reasonable objective because although BNP has received Food and Drug Administration approval for the treatment of acutely decompensated congestive heart failure, native ANP has been shown to be 10-fold more potent than BNP in promoting cGMP production (8,9) and to have 50 times more affinity for the NPRA receptor than BNP (10). In addition, intravenous administration of ANP inhibits reperfusion injury, prevents LV remodeling, and improves LV function in patients with acute myocardial infarction (reviewed by Kasama et al. (11)).

Several attempts to exploit expected beneficial actions of elevated NP blood levels in a chronic setting such as essential hypertension and chronic congestive heart failure have been made. For various reasons, including insufficient or undesirable effects, attempts to decrease the catabolic rate of NP, and hence increase their circulating levels through the use of pharmacological agents that inhibit the NP-degrading enzyme neutral endopeptidase 24.11 or agents that combine this property with angiotensin-converting enzyme inhibitor activity, have not prospered so far. Mimicking compounds that would effectively activate the NPRA receptor have not been reported nor have compounds that would increase the sensitivity of this receptor to their natural ligands. An alternative approach—the development of recombinant proteins that fuse NP to serum albumin while preserving NP activity and greatly increasing half-life—may prove of particular interest (12). Lastly, modifications in the ANP molecule with the purpose of increasing its potency or biological half-life would likely remain a target of development after the findings reported by McKie et al. (6).

Of central importance is that the diverse pharmacological properties of ANP amount to a combination of the pharmacological properties of the different compounds making up the complex and expensive polypharmacy now used to treat acute myocardial infarction and congestive heart failure. What is more, ANP exerts these effects while simultaneously preventing deleterious rebound phenomena such as the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems that occur with current drug therapies. In view of the association of mutant ANP with the above type of familial atrial fibrillation, it may well be worth investigating its molecular basis by taking into account that the storage form of ANP in the storage granules present in atrial cardiomyocytes is pro-ANP and that by extension, pro-ANP must also be a mutant form in these patients. This point acquires particular relevance when considering that...
using a yeast–2-hybrid approach, we recently demonstrated that, within the atrial cardiomyocytes, pro-ANP interacts with the calcium-activated potassium channel SK4 (13). It may be suggested that mutations in the pro-ANP molecule may cause an abnormal association with this or other ion channels, thus altering cellular targeting of such channels and potentially giving rise to pathologies in excitation or conduction.

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