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Natriuretic Peptides and Remodeling in Heart Failure

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Since the discovery of the cardiac hormone atrial natriuretic peptide (ANP) by DeBold and coworkers in 1981 [1], the field of natriuretic peptides has advanced significantly, with translation of new knowledge to the clinical practice of heart failure (HF). This new knowledge has underscored the importance of cardiorenal mechanisms that contribute to optimal cardiovascular homeostasis. Work has also established direct myocardial actions broadening their therapeutic potential beyond renal mechanisms. Indeed, one such therapeutic target is cardiac remodeling and fibrosis based upon the unique cardiorenal protective properties. The objective of this article is to review new insights into the use of natriuretic peptides as novel therapeutic agents for cardiorenal protection in progressive HF, which serves to limit cardiac remodeling and fibrosis and thus the progression of HF.

Sodium and aldosterone regulating actions of natriuretic peptides

The natriuretic peptide system consists of three known peptides that are distinct gene products: ANP and brain natriuretic peptide (BNP), which are primarily found in cardiomyocytes, and C-type natriuretic peptide (CNP), which is chiefly found in endothelial cells [2–4]. These three peptides function through the second messenger cyclic GMP (cGMP), where ANP and BNP bind to natriuretic peptide receptor A and CNP binds to natriuretic peptide receptor B (Fig. 1) [5]. All three peptides are cleared by a clearance receptor, which is a nonparticulate guanylyl cyclase–linked receptor, termed natriuretic peptide receptor C [6]. All are degraded enzymatically by widely distributed neutral endopeptidase 24.11 (NEP) [7]. Following studies in cell systems, novel mouse models of altered natriuretic peptide production or receptor disruption, integrative studies in pathophysiologic models, and in human subjects, a unifying understanding of the biology of these peptides has emerged. This unique concept of cardiorenal protection by activation of cGMP is a result of biological properties that include natriuresis, vasodilatation, inhibition of the renin–angiotensin–aldosterone system (RAAS), positive lusitropism, and inhibition of fibrosis [8–13]. Based on such an understanding, their therapeutic application has been advanced [14–19].

In HF, BNP is most potent from a therapeutic perspective in augmenting sodium excretion and exerting direct myocardial actions. This contributes to unloading of the heart and improving congestion. Specifically, in a model of severe HF, we have demonstrated that BNP is markedly more potent in augmenting sodium excretion compared with ANP or the renally altered form of ANP, which is Urodilatin [20]. The mechanism of this greater natriuretic action is explained by greater glomerular filtration rate (GFR)-enhancing actions and decrease in terminal nephron sodium reabsorption. We speculate that the

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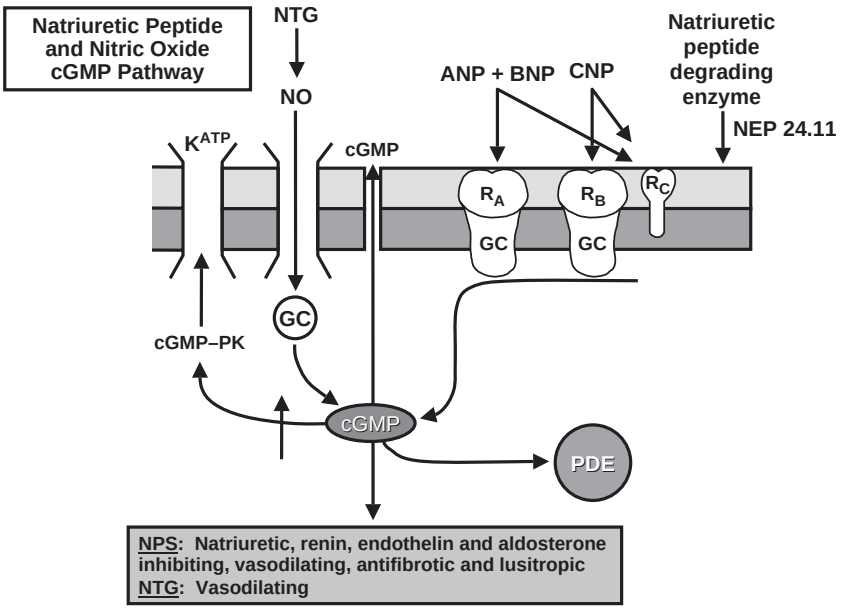

Fig. 1. Natriuretic peptide and nitric oxide cGMP pathway.

more potent renal actions of BNP may be explained by a greater resistance to NEP degradation secondary to its more extended C-terminus as compared with ANP. CNP lacks natriuretic actions [21].

This renal-enhancing action of BNP has understandable importance in developing BNP-based therapies for the treatment of HF. Increasing evidence supports the concept that the kidney plays a key role in HF, because the presence of reduced GFR is the most robust marker for poor survival, more so than even New York Heart Association class or ejection fraction [22]. Indeed, the concept of enhancing renal function in HF has emerged as an important therapeutic strategy to delay disease progression [23]. Furthermore, the development of renal resistance to the natriuretic peptides may be an ominous sign of very high risk for increased mortality [24,25].

Natriuretic peptide receptor A, to which both ANP and BNP bind, is highly expressed in the adrenal gland [26,27]. One of the first demonstrations of the biologic action of ANP was its inhibition of aldosterone (ALDO) synthesis and release and that of angiotensin II stimulated increases in ALDO [28,29]. As a potential therapeutic strategy in HF, with the exception of direct ALDO receptor antagonists, there is no other biologic factor that has such functionally important direct ALDO-suppressing properties. Based on the renal sodium retaining and fibrotic actions of ALDO, the clinical use of the cardiac natriuretic peptides in HF deserves special consideration.

Fig. 2 illustrates the recent findings of Cataliotti and coworkers [30] in which the coadministration of intravenous BNP at a high dose and intravenous furosemide enhanced GFR, which was not observed with furosemide alone in a model of overt HF. Furthermore, low- and high-dose BNP plus furosemide demonstrated a greater diuretic and natriuretic response. Most importantly, there was a lack of activation of ALDO with coadministration of BNP and furosemide, in contrast to marked activation of ALDO with the loop diuretic alone. Not illustrated is the greater unloading of the heart, which occurred with coadministration of both sodium-regulating compounds. This study underscores the potential benefit of chronic BNP therapy in HF to modulate ALDO, enhance renal sodium and water excretion, and maintain GFR. These findings were also supported by our investigations with the natriuretic peptide-based therapeutic agent omapatrilat, which simultaneously inhibits NEP and ACE [31]. Specifically, in a model of early stage HF, we observed that omapatrilat administered with furosemide was superior in enhancing renal function, unloading the heart, and inhibiting activation of ALDO compared with ACE inhibition with a diuretic. Therefore, BNP possesses novel renal and ALDO-regulating properties, and both natriuretic peptide–based therapies