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The natriuretic peptides and cardiometabolic health

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Abstract

Natriuretic peptides are cardiac-derived hormones with a range of protective functions, including natriuresis, diuresis, vasodilation, lusitropy, lipolysis, weight loss, and improved insulin sensitivity. The actions are mediated through membrane bound guanylyl cyclases that lead to production of the intracellular second-messenger cGMP. A growing body of evidence demonstrates that genetic and acquired deficiencies of the natriuretic peptide system can promote hypertension, cardiac hypertrophy, obesity, diabetes mellitus, the metabolic syndrome, and heart failure. Clinically, natriuretic peptides are robust diagnostic and prognostic markers and augmenting natriuretic peptides is a target for therapeutic strategies in cardio-metabolic disease. This review will summarize current understanding and highlight novel aspects of natriuretic peptide biology.

Keywords

natriuretic peptides; guanylyl cyclase; cardio-metabolic; genetics; neprilysin

Natriuretic peptides and their receptors

The natriuretic peptides are a family of cardiac-derived hormones that have pleiotropic cardiometabolic protective effects.[1] Three natriuretic peptides, atrial (ANP), B-type (BNP), and C-type (CNP) have been described, with ANP being the first, identified by de Bold and colleagues and sequenced by Matsuo and Kangawa.[2–7] In humans, these peptides are encoded by the *NPPA* (natriuretic peptide precursor A) and *NPPB* genes located in tandem on chromosome 1, and *NPPC* on chromosome 2.[8–10] Mechanical stretch of cardiomyocytes and/or stimulation by endothelin, angiotensin II, the sympathetic nervous system, vasopressin, hypoxia, cold, or exercise induces the transcription factor GATA to bind the natriuretic peptide promoters.[3, 11] The natriuretic peptide precursor genes are transcribed and translated into preprohormones that undergo post-translational processing and cleavage into biologically active carboxy-terminal and inactive amino-terminal fragments by the serine proteases corin and/or furin (Figure 1).[12] ANP is predominantly synthesized, stored in

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preformed granules, and released from atrial cardiomyocytes; BNP is produced in atrial and ventricular cardiomyocytes; and CNP is largely derived from vascular endothelial cells and neurons.[13–15] The bioactive carboxy-terminal natriuretic peptides have relatively short half-lives in the circulation, while the inactive amino-terminal fragments are more stable with longer half-lives.[16]

The natriuretic peptides exert their actions by binding guanylyl cyclase receptors A (GC-A for ANP and BNP) and B (GC-B for CNP), which are transmembrane proteins that catalyze the conversion of intracellular guanosine triphosphate into cyclic guanosine monophosphate (cGMP), which then increases intracellular protein kinase G (Figure 2).[17] Natriuretic peptide receptor C (NPR-C) functions predominantly as a clearance receptor for all three natriuretic peptides, but also exerts effects on inhibitory G-proteins and adenylyl cyclase with activation of phospholipase C.[18] Receptors for the natriuretic peptides are not only present on cardiomyocytes and fibroblasts, but also the kidneys, vascular and gastrointestinal smooth muscle, adrenals, brain, pancreas, adipocytes, chondrocytes, platelets, and the liver, suggesting that natriuretic peptides have biologic actions beyond natriuresis. In addition to clearance through NPR-C, natriuretic peptides are inactivated by neutral endopeptidases located within renal tubular cells and the vasculature, as well as insulin degrading enzyme and dipeptidyl peptidase-IV, and may also be passively excreted in the urine (Figure 1).[12]

Biologic effects of natriuretic peptides: experimental evidence

Genetic models

Experimental evidence supports the broad range of cardiovascular and metabolic actions of the natriuretic peptides. Transgenic overexpression or knock-out mouse models for each of the natriuretic peptides and their receptors provides consistent evidence of these hormones protective cardio-metabolic effects (Table 1).[11] Overexpression of *NPPA, NPPB*, and *GC-A* leads to blood pressure lowering and protection against salt-sensitive hypertension.[19–22] Knockout of *NPR-C* yields a similar phenotype of lower blood pressure.[23] Mice overexpressing the BNP gene (*NPPB*) are also resistant to obesity and demonstrate lower glucose and insulin concentrations compared with wild-type mice, a finding attributed to increased skeletal muscle mitochondrial content and fatty acid oxidation.[24–26] In contrast, *NPPA, NPPB*, and *GC-A* knockout mice exhibit hypertension, salt-sensitivity, cardiac hypertrophy, cardiac fibrosis, and susceptibility to heart failure, as well as obesity.[27–37] Alterations in the corin protein (corresponding to known human genetic variants) that lead to reduced cleavage of natriuretic peptide prohormone into the active peptide also result in salt-sensitive hypertension and cardiac hypertrophy.[38, 39]

Non-genetic experiments

In vitro experiments and in vivo data highlight the role of the natriuretic peptides in cardiovascular and metabolic physiology. Animals exposed to infusion of ANP or BNP have lower blood pressure, not only through increased natriuresis and diuresis, but also through arterial and veno-dilation, increased vascular permeability (shifting volume from the intracellular to extracellular space), and direct suppression of the renin-angiotensin-aldosterone and sympathetic nervous systems.[3, 40, 41] CNP administration induces marked

venodilation.[3] The natriuretic and diuretic effects are due to 1) enhanced glomerular filtration through simultaneous dilation of afferent arterioles and constriction of efferent arterioles and 2) direct effects on renal tubular cells through antagonism of angiotensin II and vasopressin.[42–44] The vasodilatory effects of ANP and BNP are also mediated centrally in the brainstem through decrease of sympathetic outflow.[41, 45, 46]

ANP inhibits growth of cardiac fibroblasts and can induce cardiomyocyte apoptosis.[47–49] Similar to ANP, CNP is a potent inhibitor of cardiac fibroblasts and exerts anti-fibrotic effects,[50] which may be in part mediated by PKG dependent phosphorylation of Smad3 resulting in less nuclear translocation when stimulated by transforming growth factor-β.[51] Through p38 MAPK, natriuretic peptides also exhibit anti-mitogenic properties with some indication of anti-neoplastic potential through reduction of inflammation and cell adhesion processes as well.[52, 53]

The p38 MAPK pathway may also modulate the effect of natriuretic peptides on the induction of brown adipose tissue from white adipocytes.[54] Further supporting a role for the natriuretic peptides in the control of energy homeostasis, exposure of cultured adipocytes to physiologic doses of ANP and/or BNP promote cGMP dependent activation of hormone sensitive-lipase leading to lipolysis.[55,56]

Biologic effects of natriuretic peptides: clinical evidence

Genetic variants

The biologic importance of the natriuretic peptide system is supported by the finding that the *NPPA* gene is highly conserved across species.[57] Nevertheless, genetic variants in the natriuretic peptides, their receptors, and activating proteases have been identified in humans and their associations with cardio-metabolic phenotypes described.[57] The results of these genetic variation studies in humans parallel the evidence from animal models regarding the role of the natriuretic peptide system.

A number of variants in the promoter, coding, intronic, and 3' untranslated region of the *NPPA* gene have been characterized (Table 2).[57] Candidate gene studies in Japanese and Italian individuals have associated a C-664G variant with lower circulating ANP, hypertension, and left ventricular hypertrophy.[58,59, 60] There are mixed data regarding another missense variant, rs5063, which results in a valine to methionine substitution and has been linked to lower blood pressure among Chinese individuals and participants in the Women's Genome Health study, although this was not observed among Japanese individuals.[58, 61,62, 63] In other populations, the rs5063 variant was associated with an increased risk of hypertension or stroke.[64, 65,66] Interestingly, the rs5065 (2238 T>C) variant in exon 3 has been associated with a decreased risk of hypertension,[67] but higher risk of myocardial infarction and stroke, that may be mediated through altered NPR-C activation and resultant endothelial dysfunction.[68–72] Nonetheless, many of the aforementioned candidate genes have not been reliably reproduced in large-scale population genetic studies nor in meta-analyses of GWAS studies.

The most statistically robust findings to date have derived from studies of white individuals, given the larger sample sizes. For instance, from a meta-analysis of data from the Framingham Heart Study, the Malmo Diet and Cancer Study, and the Finrisk study, the rs5068 A/G variant in the 3' untranslated region of the *NPPA* gene is associated with higher circulating ANP levels at a genome-wide level of significance (among carriers of the minor allele, G, $P = 8 \times 10^{-70}$). The G allele has been associated with lower blood pressure, less hypertension, and less ventricular hypertrophy.[73, 74] Additional studies demonstrate that the rs5068 A/G variant relates to a favorable metabolic profile as evidenced by lower body mass index, smaller waist circumference, higher HDL, lower C-reactive protein, as well as less susceptibility to heart failure.[75, 76] Recently, Arora and colleagues elucidated the molecular mechanism by which the rs5068 variant influenced ANP production. The variant is in the non-coding 3' UTR of the *NPPA* gene, a region that is targeted by micro-RNAs. ANP expression was modulated through negative regulation by a specific microRNA, miR-425, which binds to the site of rs5068. Thus, individuals with the AG allele combination are resistant to miR-425, and therefore have higher circulating ANP levels and less hypertension compared with AA homozygote individuals.[77]

Genetic variants in other natriuretic peptide and related genes have also been described. The rs198388 (presence of A allele) and 198389 (presence of the C allele) variants in the *NPPB* gene are associated with lower blood pressure, improved left ventricular diastolic function, reduced left ventricular remodeling, and lower risk of diabetes mellitus.[73, 78–81] A functional deletion mutation in the 5' flanking region of the natriuretic peptide receptor *GC-A* gene reduces transcription and is associated with hypertension and ventricular hypertrophy among Japanese individuals.[82] In genome wide association studies, *NPR-C* variants are associated with hypertension in Caucasian and Asian individuals.[80, 81] Less is known about variants in *NPPC* and *GC-B*.[57] Missense variants in *CORIN* (555T>I and 568Q>P), which encodes a serine protease that cleaves natriuretic prohormones into the active carboxy- and inactive amino- terminal peptides, has been found to present in approximately 9% of African-Americans and is associated with a greater risk for hypertension and cardiac hypertrophy.[83, 84]

Physiologic studies

The beneficial cardiovascular effects of natriuretic peptides have also been demonstrated through infusions of ANP, BNP, and CNP. All three natriuretic peptides induce vasodilation, with ANP and BNP also lowering blood pressure.[85, 86] Infusion of ANP, BNP, or CNP may also limit post-acute myocardial infarction adverse cardiac modeling.[87–89] In the setting of heart failure, ANP and BNP infusions decrease pulmonary capillary wedge pressure and systemic vascular resistance, leading to increased stroke volume.[90–94]

Natriuretic peptides not only influence myocardial structure and function, but also exert positive influences on the vasculature. Cultured endothelial cells exposed to ANP or CNP demonstrated reduced expression of adhesion molecules (MCP-1 and P-selectin), which are needed for leukocyte infiltration into atherosclerotic plaques.[95, 96] CNP also inhibits coronary vascular smooth muscle proliferation in models of atherosclerosis,[97–99] reduces

platelet leukocyte aggregation, and limits thrombus formation through reduction in PAI-1, perhaps through NPR-C.[100_102]

The beneficial metabolic effects of natriuretic peptides have also been demonstrated in humans. Infusion of ANP at physiologic levels induced lipid mobilization from subcutaneous adipose tissue with a concomitant increase in lipid oxidation by skeletal muscle.[25, 26, 103] BNP has been demonstrated to lower glucose levels,[104] while both ANP and BNP converted white to brown fat through mitochondrial uncoupling protein-1 and p38 MAPK.[54] It has also been suggested that exercise induced lipolysis may be mediated through ANP.[105]

Epidemiologic associations

The cross-sectional associations between circulating natriuretic peptide levels and cardiovascular and metabolic disease have been examined in epidemiologic studies. An inverse relationship has been demonstrated between plasma natriuretic peptide levels and body mass index.[106, 107] Similarly, low levels of NT-proBNP and NT-proANP have been found in individuals with the metabolic syndrome and/or left ventricular hypertrophy.[108_111] The beneficial effects of natriuretic peptides on endothelial function has also been demonstrated in the Framingham Heart Study.[112] Congruent with the animal studies, low natriuretic peptide levels have been associated with the development of diabetes mellitus.[113, 114]

Natriuretic peptides as biomarkers

While experimental, population genetic, and natriuretic peptide infusion studies demonstrate inverse associations between natriuretic peptide levels and cardio-metabolic disease, clinical studies of natriuretic peptides as prognostic biomarkers typically yield positive associations between circulating natriuretic peptide levels and adverse cardiovascular outcomes.[16] This apparent paradox is attributable to the fact that natriuretic peptides are counter-regulatory hormones that are released in response to cardiac stress. In population studies, higher natriuretic peptide levels, even within what might be considered a “normal” range, are commonly seen in the setting of subclinical cardiovascular disease. Thus, the elevated natriuretic peptide levels observed in clinical biomarker studies reflect normal physiologic responses to elevated cardiac wall stress.

For example, among individuals without prevalent cardiovascular disease in the Framingham Offspring Study and in Copenhagen, higher natriuretic peptide levels were positively and significantly associated with cardiovascular mortality[115] or major adverse cardiovascular events,[116] respectively. Among persons with stable coronary artery disease or acute coronary syndromes, higher natriuretic peptides were significantly and positively associated with greater risk for recurrent cardiovascular events and/or death.[117_121] Similarly, higher natriuretic peptide levels are associated with worse outcomes among individuals with heart failure.[122_125] However, further evidence for the beneficial effects of natriuretic peptides, even in the setting of subclinical or over cardiovascular disease, comes from therapeutic trials in which augmentation of natriuretic peptides led to favorable cardiovascular effects.

Natriuretic peptides as a therapeutic target

Most strategies for the prevention and treatment of cardiovascular disease have been directed at blocking the deleterious effects of the renin-angiotensin-aldosterone axis and sympathetic nervous system.[12] Given that hypertension, obesity, and insulin-resistance are major risk factors for the development of cardiovascular disease and natriuretic peptides guard against the development and progression of these disorders, natriuretic peptides are attractive therapeutic targets (Figure 3).

Therapeutic approaches have included intravenous infusions of recombinant ANP or BNP, oral inhibitors of neutral endopeptidases, and synthetic or “designer” natriuretic peptide analogues.[3] Intravenous infusions of ANP and BNP have been tested in clinical trials for hypertension[126] and heart failure with favorable hemodynamic effects, but no clear benefit on long-term clinical outcomes.[94, 127] Furthermore, oral formulations of ANP and BNP are not stable, currently limiting their therapeutic application in chronic disease.

An alternative strategy to direct supplementation of natriuretic peptides is to limit the breakdown of endogenous natriuretic peptides. Inhibitors of neutral endopeptidases are stable when given orally and the first to be tested in hypertension was candoxatril; however, this agent was not of substantial benefit because of simultaneous vasoconstriction due to increases in endothelin-1 and angiotensin II.[128, 129] Subsequently, combined inhibition of neutral endopeptidases and angiotensin converting enzyme with omapatrilat was evaluated in hypertensive and heart failure patients in the OCTAVE, OVERTURE, and IMPRESS trials. Blood pressure was lower in omapatrilat treated patients compared to those treated with enalapril alone; however, omapatrilat was associated with a higher frequency of angioedema and symptomatic hypotension, without demonstration of superior efficacy, thereby preventing approval for clinical use.[130–132] More recently, neutral endopeptidase inhibition has been combined with angiotensin receptor blockade to avoid the angioedema seen with ACE inhibition. The angiotensin receptor and neprilysin inhibitor (ARNI) LCZ696 is efficacious for lowering blood pressure among patients with essential hypertension, without increased angioedema compared with valsartan alone.[133] In a phase II study of heart failure with preserved ejection fraction patients (PARAMOUNT), LCZ696 was superior to valsartan alone in reducing NT-proBNP levels over 12 weeks of follow up.[134] Recently, LCZ696 was demonstrated to be superior to enalapril for reducing cardiovascular death and heart failure hospitalizations in patients with heart failure and reduced ejection fraction (PARADIGM-HF),[135] lending further support for the therapeutic benefit of natriuretic peptides.

“Designer” or synthetic natriuretic peptides that are more stable than native natriuretic peptides have been developed. For example, the ANP analog carperitide promotes vasodilation, natriuresis, and inhibition of the renin-angiotensin-aldosterone axis and is approved in Japan for treatment of acute decompensated heart failure.[136] Another analog, M-ANP, which is more resistant to neutral endopeptidase degradation than native ANP, has been designed and has favorable anti-hypertensive effects.[137] A novel chimeric molecule, CD-NP, has been engineered by combining the 15 amino acid carboxy-terminus of dendrapsis natriuretic peptide with CNP, resulting in a protein that is able to activate both

GC-A and GC-B. This chimeric peptide demonstrates potent natriuresis and diuresis, as well as anti-fibrotic and anti-proliferative properties.[138]

Summary

Natriuretic peptides are cardiac-derived hormones and the principal counter-regulatory system guarding against salt-retention, volume expansion, cardiac stress, and remodeling. They also modulate energy metabolism, lipolysis, weight loss, and insulin sensitivity. Low natriuretic peptide activity can be associated with increased risk for hypertension, obesity, and diabetes mellitus, conditions that are increasing in prevalence and are major risk factors for cardiovascular disease. Consequently, natriuretic peptides are attractive targets for therapeutic approaches to cardio-metabolic disease.

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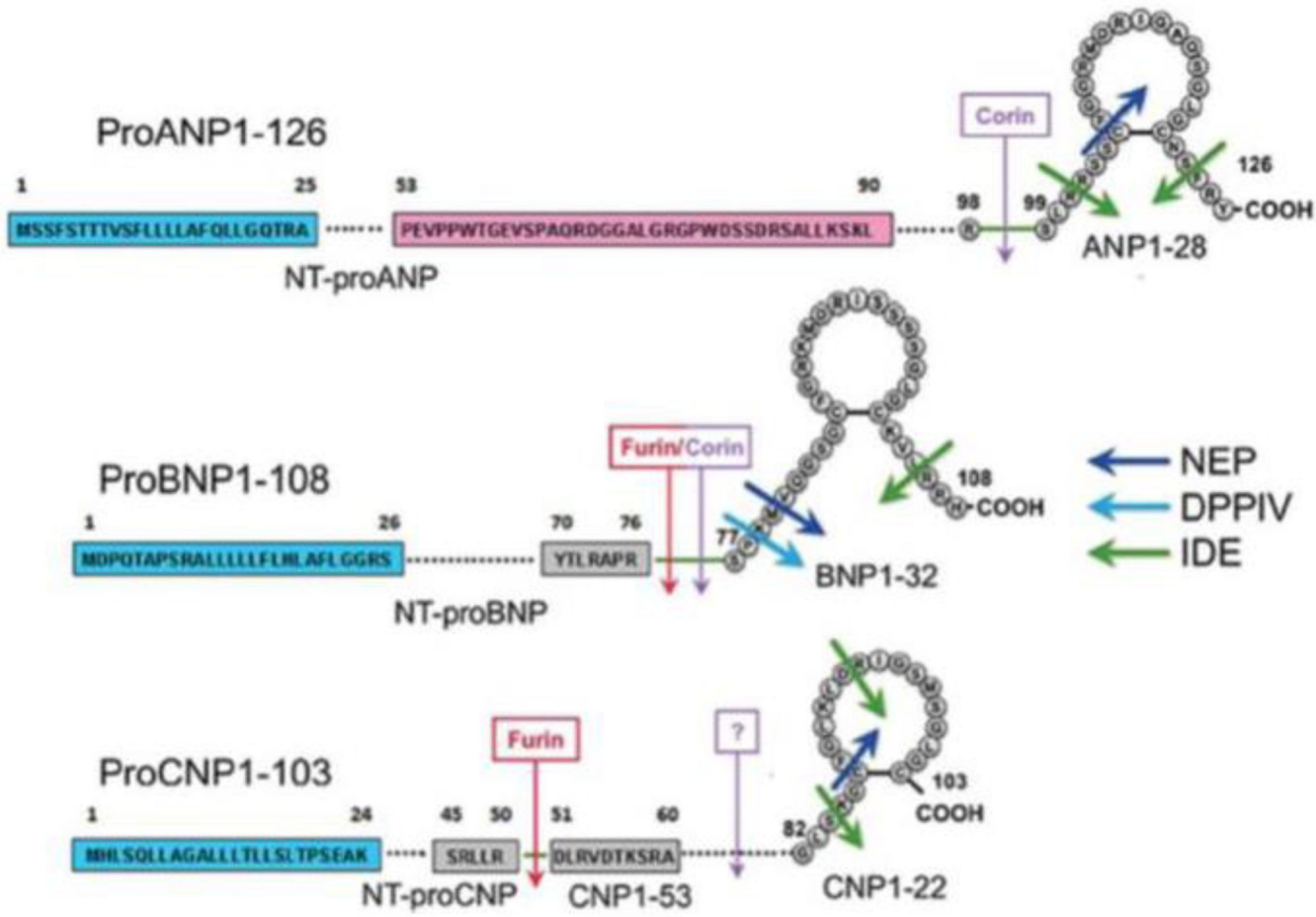

Figure 1.

The post-translational processing of natriuretic peptides. From Volpe M, Rubattu S, Burnett J, Jr. Natriuretic peptides in cardiovascular diseases: Current use and perspectives. *Eur Heart J.* 2014;35:419–425. (Permission pending)

Caption: Natriuretic peptide protein sequences and post-translational processing cleavage and degradation sites. NEP = neprilysin, DPPIV = dipeptidyl peptidase IV, IDE = insulin degrading enzyme.

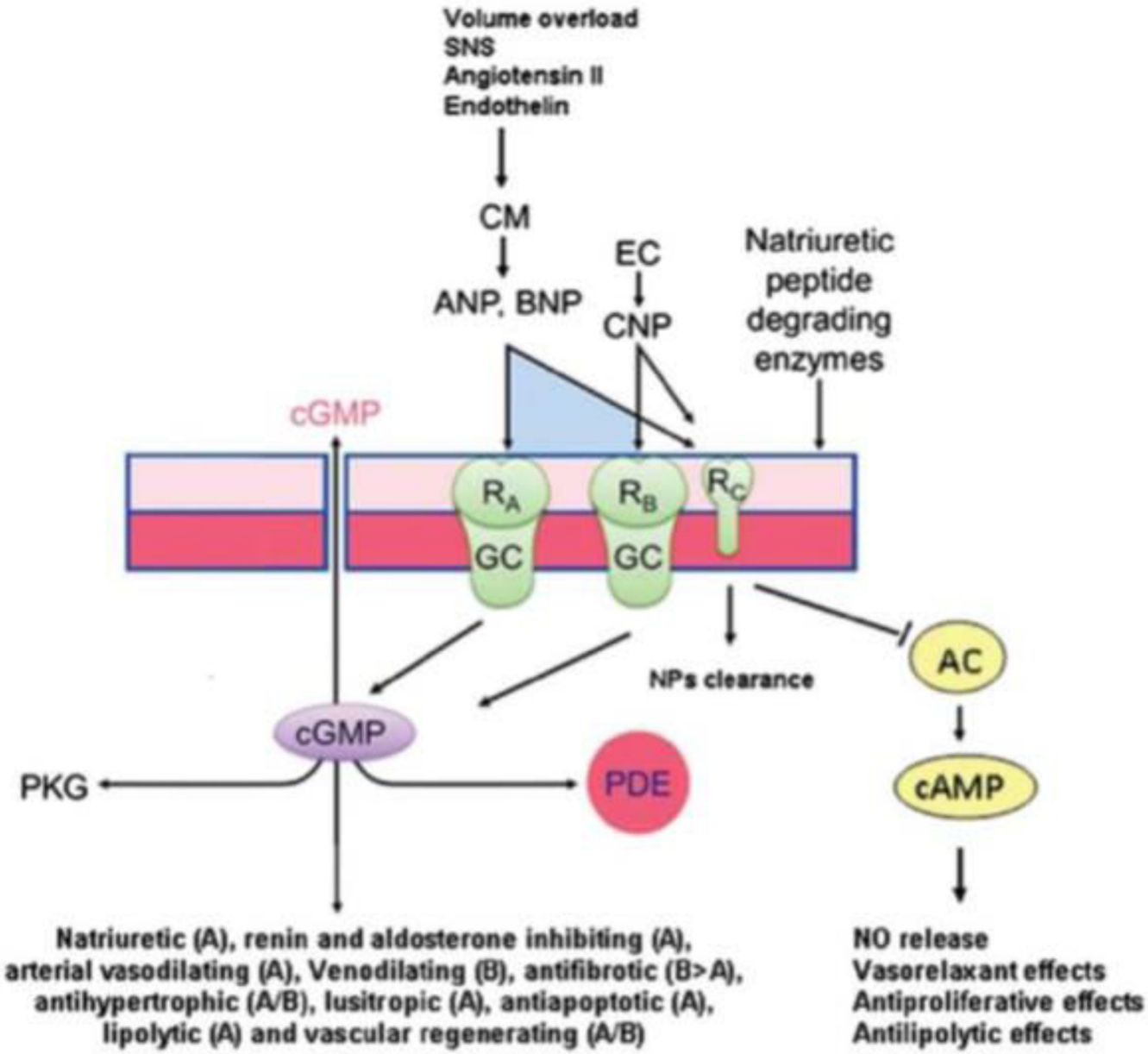

Figure 2.

The natriuretic peptide system responds to hemodynamic and metabolic stimuli through activation of guanylyl cyclase receptors resulting in cardiometabolic protect effects. From Volpe M, Rubattu S, Burnett J, Jr. Natriuretic peptides in cardiovascular diseases: Current use and perspectives. *Eur Heart J.* 2014;35:419–425. (Permission pending)

Caption: Cardiomyocytes and endothelial cells are stimulated to release natriuretic peptides, which bind receptors with guanylyl cyclase activity. This activation leads to increased intracellular cyclic GMP with beneficial downstream effects mediated through protein kinase G and phosphodiesterase. CNP also inhibits adenylate cyclase to reduce cAMP levels through the natriuretic peptide receptor-C.

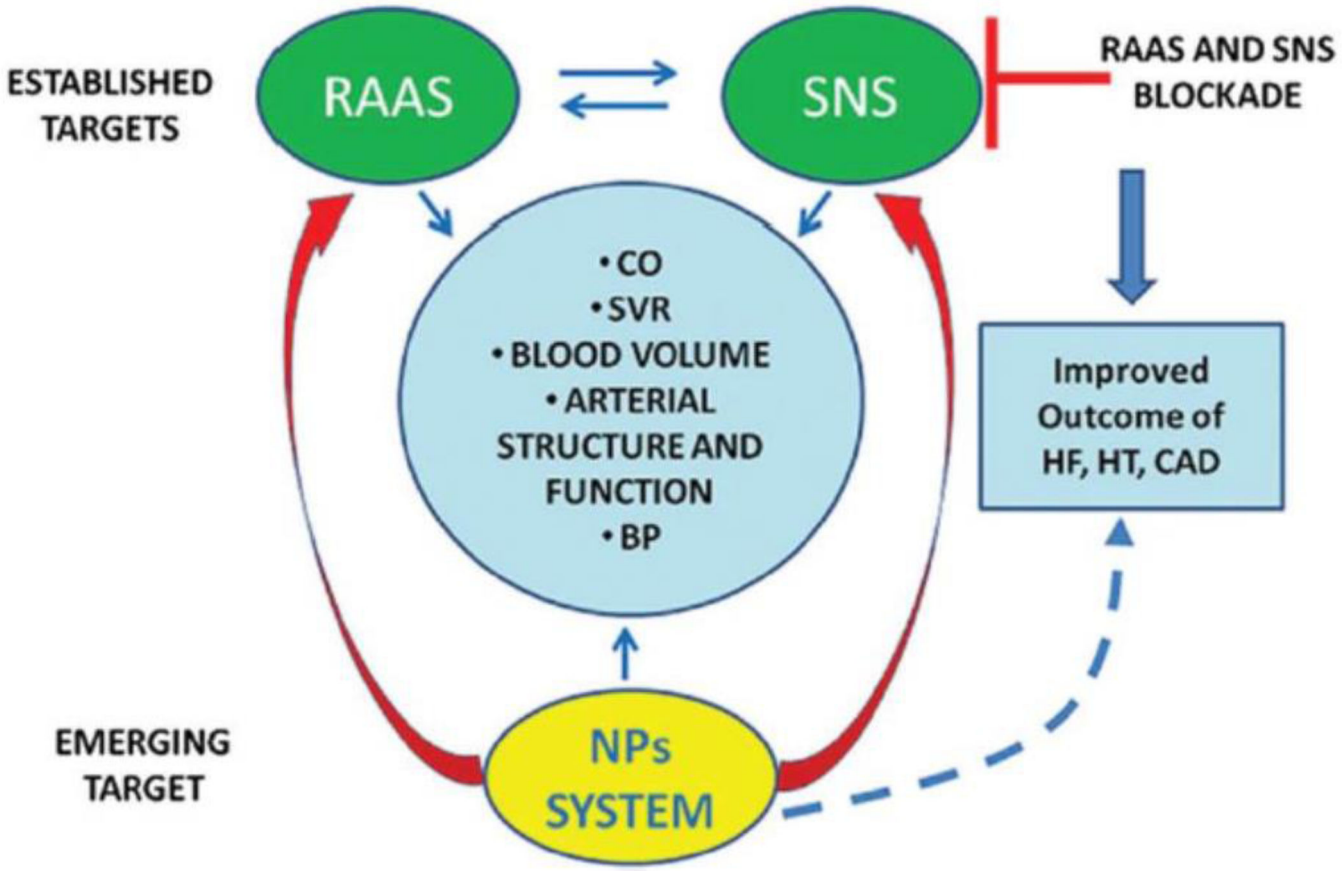

Figure 3.

Natriuretic peptides as novel therapeutic targets in cardiometabolic disease. Adapted from Volpe M, Rubattu S, Burnett J, Jr. Natriuretic peptides in cardiovascular diseases: Current use and perspectives. *Eur Heart J.* 2014;35:419–425. (Permission pending)

Caption: Natriuretic peptides exert beneficial effects on cardiac and vascular function directly and through inhibition of the renin-angiotensin-aldosterone axis and sympathetic nervous systems, making them ideal and novel targets for cardiovascular protection.

Table 1

Summary of the phenotypes associated with genetic manipulation of the natriuretic peptide system in animals. From Gardner DG, Chen S, Glenn DJ, Grigsby CL. Molecular biology of the natriuretic peptide system: Implications for physiology and hypertension. *Hypertension*. 2007;49:419–426. (Permission pending)

Gene Disruption	Phenotype/Physiology
ANP overexpression	Hypotension, decrease in hypoxic hypertension, normal salt excretion, increased H_2O intake and excretion
ANP knockout ($Nppa^{-/-}$)	Hypertension, BP-independent right and left ventricular hypertrophy, impaired Na and Cl excretion
BNP overexpression	Hypotension, skeletal overgrowth, resistance to immune-mediated renal injury
BNP knockout ($Nppb^{-/-}$)	Load dependent ventricular tibrortic lesions, no hypertrophy, no hypertension
CNP knockout ($Nppc^{-/-}$)	Dwarfism, early death
CNP overexpression (chondrocyte targeted)	Rescue of dwarfism phenotype
NPR-A (GC-A) overexpression	Hypotension, protection against salt-sensitive hypertension
NPR-A (GC-A) Knockout ($Npr1^{-/-}$)	Salt-resistant hypertension, BP-independent ventricular hypertrophy, increase in sudden death, enhanced NHE-1 activity, increased susceptibility to heart failure
NPR-A targeted knockout	
Cardiomyocyte	Hypertrophy, increase in hypertrophy markers, hypotension
Smooth muscle	Loss of ANP response, volume dependent hypertension
Vascular endothelium	Arterial hypertension and cardiac hypertrophy, increased plasma volume
NPR-B (GC-B) knockout ($Npr2^{-/-}$)	Dwarfism, neuronal disorders, female Infertility
NPR-B (GC-B) dominant-negative overexpression (rat)	BP-independent cardiac hypertrophy, increased congestive heart failure, elevated heart rate
NPR-C knockout ($Npr3^{-/-}$)	Hypotension, bone overgrowth, reduced blood volume

Table 2

Summary of *NPPA* gene variants in humans and their associated clinical phenotype. From Rubattu S, Sciarretta S, Volpe M. Atrial natriuretic peptide gene variants and circulating levels: Implications in cardiovascular diseases. *Clin Sci (Lond)*. 2014;127:1–13. (permission pending)

NPFA variant	Hypertension	LVH	cv acute events	AF	MS	HF
−664C>G	G allele more frequent in young subjects with HT [25]: C allele more frequent in Japanese subjects with HT [27]	G allele associated with increased LVH in HT [26]	No association of either allele with stroke and AMI [46,47]	No association of either allele with AF in high risk Italian patients [69]	–	–
rs5063 (664G>A)	A allele associated with lower DBP [35]: A allele associated with BP progression [36,37]; no association in japanese patients [27]	–	A allele associated with increased risk or stroke [59]; common allele associated with higher risk of acute events [53]	A allele associated with increased risk of lone AF in Chinese patients [67]; no association with AF in North American subjects [68]	–	–
Hpall	Variant allele associated with increased risk of HT [36,39]; common allele associated with increased risk of HT [40]	–	Variant allele associated with increased risk of stroke [59]	–	–	–
rs5065 (2238T>C)	C allele associated with a decreased risk of HT [41]		C allele associated with an increased risk of stroke, AMI and MACE [45–48,50]; no association with stroke [59]; no association with CV events [52]; C allele associated with a greater response to diuretic in HT [52]	No association of C allele with AF in both North American and Italian patients [68,69]		Allele variant associated with ANP plasma levels in NYHA class III–IV [71]
rs5068	Allele variant associated with a decreased risk of HT [29]	Allele variant associated with decreased occurrence of LVH [44]	–	–	Allele variant associated with a decreased risk of the MS [62,63]	No association of allele variant with HF [72]

LVH = left ventricular hypertrophy, CV = cardiovascular, AF = atrial fibrillation, MS = metabolic syndrome, HF = heart failure, HT = hypertension, AMI = acute myocardial infarction, DBP = diastolic blood pressure, BP = blood pressure, MACE = major adverse cardiovascular events.