

The Importance of Natriuretic Peptides in Cardiometabolic Diseases

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The natriuretic peptide (NP) system is composed of 3 distinct peptides (atrial natriuretic peptide or ANP, B-type natriuretic peptide or BNP, and C-type natriuretic peptide or CNP) and 3 receptors (natriuretic peptide receptor-A or NPR-A or particulate guanylyl cyclase-A natriuretic peptide receptor-B or NPR-B or particulate guanylyl cyclase-B, and natriuretic peptide receptor-C or NPR-C or clearance receptor). ANP and BNP function as defense mechanisms against ventricular stress and the deleterious effects of volume and pressure overload on the heart. Although the role of NPs in cardiovascular homeostasis has been extensively studied and well established, much remains uncertain about the signaling pathways in pathological states like heart failure, a state of impaired natriuretic peptide function. Elevated levels of ANP and BNP in heart failure correlate with disease severity and have a prognostic value. Synthetic ANP and BNP have been studied for their therapeutic role in hypertension and heart failure, and promising trials are under way. In recent years, the expression of ANP and BNP in human adipocytes has come to light. Through their role in promotion of adipocyte browning, lipolysis, lipid oxidation, and modulation of adipokine secretion, they have emerged as key regulators of energy consumption and metabolism. NPR-A signaling in skeletal muscles and adipocytes is emerging as pivotal to the maintenance of long-term insulin sensitivity, which is disrupted in obesity and reduced glucose-tolerance states. Genetic variants in the genes encoding for ANP and BNP have been associated with a favorable cardiometabolic profile. In this review, we discuss several pathways that have been proposed to explain the role of NPs as endocrine networkers. There is much to be explored about the therapeutic role of NPs in improving metabolic milieu.

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An endocrine axis between the heart and the kidneys was first established by the discovery of atrial natriuretic peptide (ANP) by Adolfo J. de Bold in 1981 [1]. The role of natriuretic peptides (NPs) in cardiovascular homeostasis has been extensively studied and well established, although much remains uncertain about the impaired natriuretic peptide signaling pathways in pathological states like heart failure. In recent years, the expression of ANP and B-type natriuretic peptide (BNP) in human adipocytes has come to light [2]. Through their role in promotion of adipocyte browning, lipolysis, lipid oxidation, and modulation of adipokine secretion, they have emerged as key regulators of energy consumption and metabolism [3]. This highlights the role of the heart as a potential endocrine “networker” for energy expenditure, which could have tremendous therapeutic implications in the management of metabolic disorders like diabetes mellitus (DM) and obesity.

Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; DM, diabetes mellitus; pGC-A, particulate guanylyl cyclase-A; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; NP, natriuretic peptide; NPR-A, natriuretic peptide receptor-A; NPR-B, natriuretic peptide receptor-B; NPR-C, natriuretic peptide receptor-C; PGC1 α , peroxisome proliferator-activated receptor-gamma coactivator-1 α .

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1. Physiology

The natriuretic peptide system is composed of 3 distinct peptides (ANP, BNP, and C-type NP or CNP) and 3 receptors (natriuretic peptide receptor-A or NPR-A or particulate guanylyl cyclase-A [GC-A], natriuretic peptide receptor-B or NPR-B or particulate guanylyl cyclase-B, and natriuretic peptide receptor-C or NPR-C or clearance receptor) [4].

A. Natriuretic Peptides

In humans, ANP is a 28-amino acid peptide and BNP is a 32-amino acid peptide. ANP is predominantly secreted from the heart as a cardiac hormone in response to atrial stretch. BNP has 2 dominant molecular forms: proBNP-108 and BNP-32. BNP-32 is dominant in the atrial tissue, whereas proBNP-108 is dominant in the ventricular tissue [5]. ProBNP-108 is cleaved into BNP-32 and NT-proBNP-76 as it is secreted. ANP levels increase in response to elevated atrial pressures, whereas BNP is a reflection of ventricular overload [4].

Mechanical stretch and stress of atrial and ventricular walls are potent inducers of ANP and BNP, respectively. In addition, animal model studies have suggested that myocardial ischemia and hypoxia also stimulate ANP and BNP secretion independent of myocardial stretch [6]. Several humoral factors, including angiotensin II, endothelin-1, thyroid hormones, glucocorticoids and sex steroids, inflammatory cytokines like interleukin-1 and -6, and tumor necrosis factor- α , have also been shown to modulate ANP and BNP secretion [2].

The physiological role of CNP in vascular and heart tissues has garnered significant attention in recent years. It is detected in low levels widely in the central nervous system, endothelium, kidney, bone, and heart [7]. CNP is translated as a 126-amino acid prepropeptide and processed, likely via enzyme furin, into NT-proCNP, CNP-53, and CNP-22. CNP-22 is rapidly degraded and is reported to have a very short half-life of 2.6 minutes in humans. CNP-53 is the most biologically active and has a longer half-life than CNP-22. Endothelial CNP plays a key role in vascular homeostasis [8]. Within the cardiac tissue, it has antihypertrophic effects on cardiac myocytes and antifibrotic effects on fibroblasts [9].

B. Natriuretic Peptide Receptors

The NP receptors NPR-A and NPR-B catalyze the synthesis of a classic intracellular second messenger, cyclic guanosine monophosphate or cGMP [2]. cGMP binds to proteins like cGMP-dependent protein kinases, cGMP-binding phosphodiesterases, and cyclic nucleotide-gated ion channels [10]. NPR-C controls the concentrations of NPs through receptor-mediated internalization and degradation [10], and NPR-A to NPR-C ratio plays a role in regulating the biological activity of NPs [11]. In addition to its clearance activity, NPR-C also possesses intrinsic activity regulating endothelial function [12], with the CNP/NPR-C signaling pathway playing a fundamental role in regulating vascular tone [8]. The binding of CNP to NPR-C has also been shown to exert a negative inotropic effect on cardiac myocytes via its inhibitory action on adenylyl cyclase activity, which inhibits L-type calcium channels through decreased cytosolic cyclic adenosine monophosphate concentrations and protein kinase A activity [9]. Animal models have demonstrated vascular relaxation and drop in blood pressures associated with administration of NPR-C agonists [7].

The other major process of degradation of NPs is mediated by the enzyme neutral endopeptidase 24.11 (neprilysin) [10, 13] (Fig. 1).

C. Natriuretic Peptides and Cardiovascular Homeostasis

ANP and BNP are thought to function as defense mechanisms against ventricular stress and the deleterious effects of volume and pressure overload. They are stored together in atrial granules and secreted into the circulation in response to myocardial stretch [3]. They protect the heart from high preload and afterload by promoting diuresis and natriuresis, as

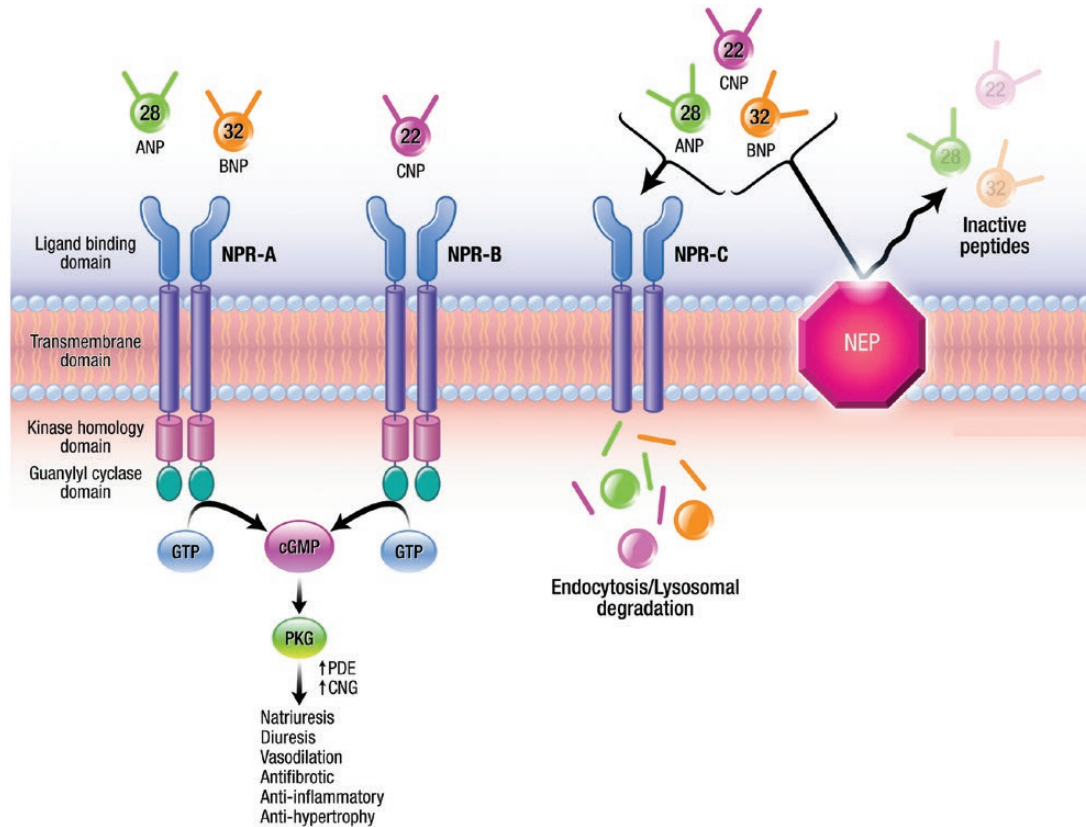


Figure 1. Action of natriuretic peptides and receptors in target cells to maintain cardiovascular homeostasis. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; CNG, cyclic nucleotide-gated ion channel; CNP, C-type natriuretic peptide; GTP, guanosine-5'-triphosphate; NEP, neprilysin; NPR-A, natriuretic peptide receptor-A; NPR-B, natriuretic peptide receptor-B; NPR-C, natriuretic peptide receptor-C; PDE, cGMP-binding phosphodiesterases; PKG, cGMP-dependent protein kinases.

well as inducing vasodilation [2]. ANP and BNP both reduce sympathetic tone and suppress renin and aldosterone secretion. The coordinated endocrine action of the NP/guanylyl cyclase system not only regulates systemic blood pressure and intravascular volume, but also plays a role in the modulation of pulmonary artery pressure and exerts local cardiac effects that counteract cardiac hypertrophy and fibrosis [3].

CNP elicits a negative inotropic response in the cardiac myocardium via the NPR-C pathway—mediated inhibition of adenylyl cyclase activity. In addition, it has been shown to exert a positive lusitropic effect via the NPR-B/cGMP pathway by amplifying the signaling of the beta-1 adrenergic receptor in chronic heart failure [9]. Endothelial CNP regulates reactivity of circulating leukocytes and platelets, systemic blood pressure, as well as distal arteriolar and capillary blood flow by exerting cGMP-mediated vasodilatory effects [14, 15]. Endothelium-derived CNP has also been shown to play a role in angiogenesis and vascular remodeling after ischemia through its NPR-C-mediated actions, suggesting a therapeutic potential in peripheral arterial disease and other ischemic cardiovascular disorders [15, 16]. Lastly, CNP also plays a role in regulation of heart rate and electrical conduction in the heart through its action on the L-type calcium channels in the sinoatrial node [16].

2. Natriuretic Peptides and Heart Failure

It is well established that patients with heart failure have elevated levels of ANP and BNP that correlate with disease severity. To explain the increased levels of these cardioprotective

peptides in diseased states, several mechanisms have been described. Heart failure is associated with upregulation of proANP and proBNP with relative corin deficiency, an enzyme that is crucial for appropriate processing of NPs, thus leading to high circulating levels of unprocessed and poorly active NPs [17, 18]. Secondly, there is increased enzymatic degradation of NPs through enhanced activity of neprilysin, the peptidase that inactivates NPs. This is supported by recent clinical observations that neprilysin inhibition leads to reduced risk of hospitalization and death in heart failure patients [19]. Other mechanisms that have been postulated include increased NP cellular internalization by NPR-C, desensitization of the GC-A receptor, alteration of intracellular GC-A signaling pathways, and enhanced intracellular degradation of cGMP by phosphodiesterases 5 and 9 [3]. Target organ responsiveness to NPs is also diminished because of desensitization of NP receptors as well as reduced expression of receptors in cardiomyocytes, intramyocardial vessels, and peripheral vascular beds. In addition, overactivation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and endothelin-1, all of which are antagonistic to the NP system, is seen in chronic heart failure [20]. Paulus and Tschöpe suggested a novel paradigm in the development of heart failure with preserved ejection fraction (HFpEF)—suggesting a systemic inflammatory state induced by obesity or DM, for example, causing oxidative stress, which leads to decreased myocardial nitric oxide bioavailability. This, in turn, leads to reduced protein kinase G activity, which is involved in the NP intracellular signaling pathway. This results in stiff and hypertrophied ventricles [21]. Myocardial BNP expression is also lower in HFpEF than HFrEF [22], suggesting that drugs which increase BNP levels could be a potential therapeutic strategy for HFpEF.

A. Diagnostic and Prognostic Significance of Natriuretic Peptides

The role of NT-proBNP as a predictive biomarker of all-cause and cardiovascular mortality, independent of confounders, has been well established, with a predictive value comparable to that of microalbuminuria [23]. Even small increases in baseline BNP levels were strong predictors both of left ventricular (LV) hypertrophy and diastolic dysfunction [24].

Studies have shown heart failure to be associated with increased levels of proBNP-108 in addition to BNP-32 and NT-proBNP-76 [25]. ProBNP-108 does not induce cGMP production as effectively as BNP-32. The ratio of proBNP-108 to BNP-32 is also markedly increased in patients with decompensated heart failure. The increase in proBNP-108 in heart failure, which is considered hormonally less active, results in a relative deficiency in NP, despite the total increase in the measured assay [5]. Most commercial assays cross-react with inactive or poorly active BNP-related peptides like proBNP, BNP 3-32, and junk-BNP. Patients with heart failure have an increased proportion of inactive proBNP, which contributes to reduced effectiveness of circulating BNP, impairing the compensatory actions and causing progression of heart failure [26]. Abnormalities in NP processing have also been demonstrated in prior studies—with an increase in the level of *O*-glycosylated proBNP but not proBNP seen in proportion to severity of heart failure [27, 28]. Increases in the levels of such hormonally less active peptides leads to an attenuation in the increase of cGMP, seen in patients with severe heart failure [4].

Despite these limitations, NPs play an important clinical role in management of heart failure. The GUIDE-IT [29] trial randomly assigned patients with heart failure with reduced ejection fraction (HFrEF) (< 40%), elevated NP levels, and a history of prior heart failure event to either an NT-proBNP-guided strategy (medical therapy titrated with the goal of achieving NT-proBNP < 1000 pg/mL) vs usual care. The study found no difference between the 2 arms. Of note, the achieved decreases in NT-proBNP levels were not significantly different between the 2 groups. On the other hand, another recent trial demonstrated that biomarker-guided intensified treatment was associated with a 65% reduction in risk of hospitalization or cardiac death in patients with DM, NT-proBNP greater than 125 pg/mL, and no known cardiac disease [30]. Thus, the present data are conflicting and call for more clinical trials with improved generalizability.

B. Natriuretic Peptides as Therapeutic Agents

In recent years, the angiotensin receptor-neprilysin inhibitor (sacubitril-valsartan) has been shown to be clinically beneficial in patients with HFrEF [31]. The benefits conferred by this drug in heart failure may be, in part, secondary to potentiating of the NPs. However, the exact mechanism remains unresolved. Synthetic ANP (also known as anaritide or carperitide) and human recombinant BNP (nesiritide) have been studied for their therapeutic role in hypertension and heart failure. Nesiritide has a significantly longer half-life than anaritide and is thought to be the better of the 2 drugs [10]. Carperitide infusions resulted in elevated sodium and water excretion along with decreased blood pressure in patients with hypertension [32] and chronic heart failure [33]. Nesiritide infusions have been associated with vasorelaxation, natriuresis, diuresis, and decreased plasma aldosterone and endothelin levels [34, 35]. Chronic subcutaneous BNP administration has been shown to improve LV remodeling, decrease LV-filling pressures, and suppress renin angiotensin while preserving glomerular filtration rate [36]. Wan et al also showed that in patients with preclinical diastolic dysfunction, chronic BNP administration led to sustained improvement in diastolic dysfunction without development of tachyphylaxis to the enhanced cardiorenal response to acute volume loading [37]. In light of these promising clinical outcomes, longer half-life BNP formulations are currently under development [38]. Although the U.S. Food and Drug Administration approved the use of nesiritide for acute decompensated heart failure in 2001, there has been some concern about increased risk of renal injury [39] and mortality [40] associated with this. This was refuted by the ASCEND-HF [41] trial, which demonstrated no increase or decrease in the rate of death, rehospitalization, or worsening renal function with the use of nesiritide. It was associated with a small, nonsignificant effect on dyspnea when used in combination with other therapies and also with an increase in the rates of hypotension. The ROSE trial by Chen and colleagues also demonstrated that neither low-dose nesiritide nor low-dose dopamine enhanced decongestion or improved renal function in patients with acute heart failure and renal dysfunction when added to standard diuretic therapy [42].

CNP does not stimulate natriuresis at physiological concentrations, and its potential therapeutic role in cardiovascular diseases is yet to be explored [10]. However, there has been recent evidence suggesting it can prevent cardiac remodeling after an acute myocardial infarction in mice [43].

3. Natriuretic Peptides in Cardiovascular and Metabolic Cross-Talk

The discovery of the potent lipolytic effects of NPs in 2000 has led to an expansion of our understanding of their role beyond blood pressure and volume control. NPs control fatty acid mobilization from adipocytes as well as mitochondrial biology and cellular energy metabolism in adipocytes and skeletal myocytes [13].

A. Role of Natriuretic Peptides in Fat Metabolism and Glucose Handling

The NPR-A–mediated rise in cGMP and activation of protein kinase G leads to phosphorylation of hormone-sensitive lipase and perilipin, which in turn activates lipases and triggers lipolysis [44]. NPR-A activation also induces transcription of genes, leading to enhanced energy expenditure and adipocyte browning [45], modulates adipokine secretion, and has a beneficial effect on adipose inflammation and insulin resistance [2]. Several pathways have been proposed—activation of the p38 mitogen-activated protein kinase-activating transcription factor-2 and PGC1 α (peroxisome proliferator-activated receptor- γ coactivator-1 α) pathways seem to be involved [13] (Fig. 2). To further the hypothesis of a “gut-heart link,” the glucagon-like peptide-1 receptors in the atrial myocardium, which are activated by a nutrient-rich meal, induce ANP secretion, thus indirectly leading to metabolic and hemodynamic changes [46]. In addition, CNP also reduces food intake and body weight through activation of the hypothalamic melanocortin pathway [47].

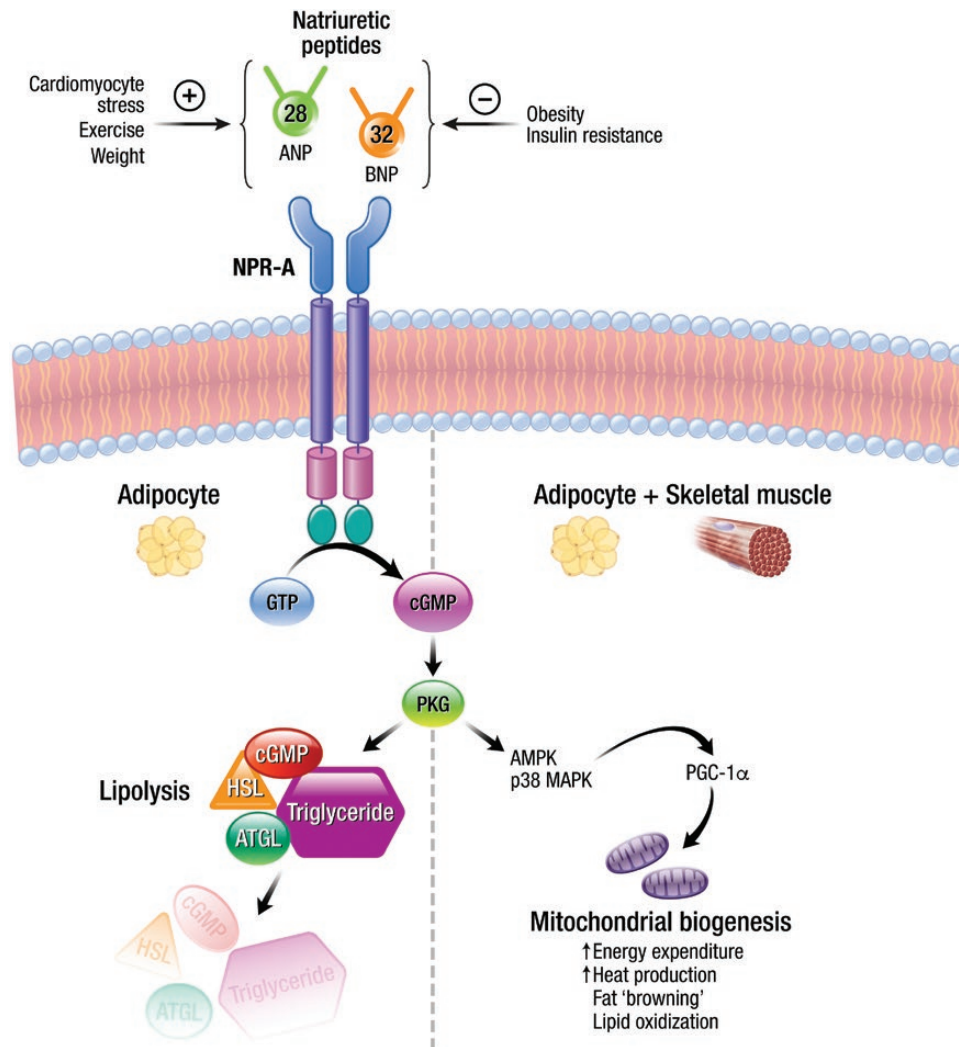


Figure 2. Role of natriuretic peptides in fat metabolism and glucose handling. AMPK, 5' adenosine monophosphate-activated protein kinase; ANP, atrial natriuretic peptide; ATGL, adipose triglyceride lipase; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; GTP, guanosine-5'-triphosphate; HSL, hormone-sensitive lipase; MAPK, mitogen-activated protein kinase; NPR-A, natriuretic peptide receptor-A; PGC-1 α , peroxisome proliferator-activated receptor-gamma coactivator-1 α ; PKG, cGMP-dependent protein kinases.

Coué et al demonstrated that NPR-A signaling in skeletal muscles is pivotal to the maintenance of long-term insulin sensitivity by regulating lipid oxidative capacity through a PGC1 α -dependent pathway [11]. This mechanism is disrupted in obesity and DM both in mice and human models. NPR-A is also negatively associated with total body fat and muscle total saturated ceramide content—both factors that negatively influence insulin sensitivity. In addition to the role of NPR-A, upregulation in NPR-C could also contribute to the NP-handicap in reduced glucose-tolerance states [11]. The Malmö diet and cancer study suggested that low midregional ANP levels predict development of future DM [48].

The lipolytic effects of NPs, particularly BNP [1-32], are also thought to contribute to the development of cardiac cachexia in advanced heart failure through excessive fatty acid mobilization [49]. This is supported by the inverse relationship noted between NT-proBNP and reduced abdominal fat mass in cachectic states [50].

B. Genetic Variants

ANP and BNP propeptides are encoded by the genes *NPPA* and *NPPB*, respectively. Common single-nucleotide polymorphisms in the chromosomal regions containing these genes have been associated with circulating levels of NPs, which contribute to variations in blood pressure in individuals. Associations of plasma ANP with rs5068 and rs632793, and of plasma BNP with rs5068, rs198358, and rs632793 have been identified [51]. Rs5068 and rs198358 belong to the *NPPA* gene and rs632793 belongs to the *NPPB* gene. Rs5068 is a single-nucleotide polymorphism that is most strongly associated with increased plasma ANP levels, with carriers having a 15% lower risk of hypertension. The mechanism of its effect on ANP involves interference with binding of a microRNA miR-425, which is a noncoding RNA that plays a role in the posttranscriptional regulation of gene expression [52]. This variant of *NPPA* has also been associated with a favorable cardiometabolic profile [53] with reduced systolic blood pressure, lower prevalence of myocardial infarction, lower body mass index, lower prevalence of obesity, lower waist circumference, higher high-density lipoprotein cholesterol, lower C-reactive protein, as well as a 12% reduced adjusted-risk of incident DM [54]. Another genetic variant, rs198389 within the BNP locus, has been identified to have a potential causal role in the etiology of DM, mediated by higher NT-proBNP levels [55].

C. Natriuretic Peptide–Deficient States

Several studies have recognized that obesity is associated with lower BNP concentrations [56, 57]. Multiple hypotheses have been put forward to explain this, including increased NPR-C–mediated clearance [58] as well as decreased synthesis [59]. Decreased cardiac messenger RNA expression both of ANP and BNP has been demonstrated in obese animal models. In addition, muscle NPR-A protein is dramatically downregulated in obesity and has been shown to increase in response to diet-induced weight loss [11]. The Dallas Heart Study noted that levels of BNP and NT-proBNP were inversely associated with visceral and liver fat and positively with lower gluteofemoral body fat [60]. The Atherosclerosis Risk in Communities study showed that levels of NT-proBNP in the lowest quartiles were associated with a higher risk of incident DM over a 12-year follow-up. A linear trend was also noted across the other quartiles [61].

In contrast, exercise is associated with increased circulating ANP concentrations. However, the effect on BNP appears to be less pronounced [62]. Exercise with hypocaloric dieting was found to be superior to hypocaloric dieting alone for increasing plasma levels of NT-proBNP and midregional-proANP [13]. Modest weight loss was found to reduce NPR-C messenger RNA expression, which results in decreased NP clearance [63].

Besides obesity and insulin resistance, black race/ethnicity has been identified as a state of relative NP deficiency [64, 65]. This has important physiological and clinical implications because African American individuals do have a higher prevalence of hypertension, salt sensitivity, and renal dysfunction [65].

Men have also been shown to have lower levels of NT-proBNP than age-matched women, thought to be secondary to suppression of NPs by circulating androgens [66].

D. Therapeutic Implications

Several studies have looked into the direct influence of ANP and BNP both on glucose and lipid metabolism. Studies in obese and diabetic mice have demonstrated that increasing NP levels markedly improves blood glucose control and insulin sensitivity in skeletal muscles [11]. ANP infusion in human subcutaneous tissue induces lipolysis and increases local blood flow, thus enhancing lipid metabolism [67]. Heinisch et al demonstrated that intravenous administration of BNP in healthy male individuals increased the glucose initial distribution volume and lowered plasma glucose concentrations following a glucose load, but did not affect β cell function of insulin secretion or insulin sensitivity [68]. Chronic BNP infusion was associated with a greater than 20% reduction in fasting blood glucose levels and a greater

than 15% decrease in hemoglobin A_{1c} (HbA_{1c}) in mouse models with obesity-induced impaired glucose intolerance and type 2 DM [11]. Other studies have shown BNP infusion to decrease hunger and increase satiety, thus regulating food intake control [69]. Post hoc analysis of the PARADIGM-HF trial that established the role of sacubitril/valsartan, a combination angiotensin receptor-neprilysin inhibitor, in patients with HF_{rEF} noted that patients with DM and HF_{rEF} who received sacubitril/valsartan had greater long-term reduction in HbA_{1c} when compared to those receiving enalapril, further suggesting that modulating the NP system could enhance glycemic control [70].

4. Future Directions/Clinical Implications

There is a growing body of evidence that suggests that in addition to their role in cardiovascular homeostasis, NPs have favorable effects on fat metabolism and glucose handling. NP deficiency has been associated with an increased risk of DM. Genetic variants that cause a mild elevation of NP levels translate into a lower risk of DM and metabolic syndrome. Increased NP signaling has been associated with lower blood pressure, improved oxidative metabolism and insulin sensitivity. This raises the possibility that therapeutic strategies that enhance the production/bioavailability/activity of NPs could improve the cardiovascular and metabolic milieu in individuals. For example, sacubitril/valsartan was shown to have a greater long-term reduction in HbA_{1c} when compared to enalapril in a post hoc analysis of the PARADIGM-HF trial [70]. Studies are under way for engineering of designer NPs [71] that could have improved receptor activation, resistance to enzymatic degradation, properties unique to a specific syndrome (eg, augmenting adipocyte activation in obesity), and even transcend the functional properties of endogenous NPs. Some such peptides currently in human trials include mutant atrial natriuretic peptide (MANP) (an ANP-like peptide with pGC-A-activating properties) as therapy for resistant hypertension, ANX-042 (an alternatively spliced BNP likely associated with pGC-B activation) as a potential nonhypotensive, renal enhancing treatment for heart failure, and cenderitide or CD-NP (targeting both pGC-A and pGC-B receptors) as therapy for postacute heart failure.

5. Conclusions

NPs play an important role in maintaining cardiovascular homeostasis and have a favorable effect on fat metabolism and glucose handling. Preliminary studies have proposed a causal association between an NP-deficient state and development of DM. This calls for research into potential therapeutic strategies to enhance NP production and/or activity that could potentially prevent or treat DM and obesity.

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Additional Information

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

References and Notes

1. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci.* 1981;**28**(1):89-94.
2. Gruden G, Landi A, Bruno G. Natriuretic peptides, heart, and adipose tissue: new findings and future developments for diabetes research. *Diabetes Care.* 2014;**37**(11):2899-2908.
3. Kuhn M. Molecular physiology of membrane guanylyl cyclase receptors. *Physiol Rev.* 2016;**96**(2):751-804.
4. Nishikimi T, Kuwahara K, Nakao K. Current biochemistry, molecular biology, and clinical relevance of natriuretic peptides. *J Cardiol.* 2011;**57**(2):131-140.
5. Nishikimi T, Minamino N, Ikeda M, et al. Diversity of molecular forms of plasma brain natriuretic peptide in heart failure—different proBNP-108 to BNP-32 ratios in atrial and ventricular overload. *Heart.* 2010;**96**(6):432-439.
6. Chun YS, Hyun JY, Kwak YG, et al. Hypoxic activation of the atrial natriuretic peptide gene promoter through direct and indirect actions of hypoxia-inducible factor-1. *Biochem J.* 2003;**370**(Pt 1):149-157.
7. Moyes AJ, Khambata RS, Villar I, et al. Endothelial C-type natriuretic peptide maintains vascular homeostasis. *J Clin Invest.* 2014;**124**(9):4039-4051.
8. Villar IC, Panayiotou CM, Sheraz A, et al. Definitive role for natriuretic peptide receptor-C in mediating the vasorelaxant activity of C-type natriuretic peptide and endothelium-derived hyperpolarising factor. *Cardiovasc Res.* 2007;**74**(3):515-525.
9. Matsuo A, Nagai-Okatani C, Nishigori M, Kangawa K, Minamino N. Natriuretic peptides in human heart: novel insight into their molecular forms, functions, and diagnostic use. *Peptides.* 2019;**111**:3-17.
10. Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. *Endocr Rev.* 2006;**27**(1):47-72.
11. Coué M, Badin PM, Vila IK, et al. Defective natriuretic peptide receptor signaling in skeletal muscle links obesity to type 2 diabetes. *Diabetes.* 2015;**64**(12):4033-4045.
12. Sciarretta S, Marchitti S, Bianchi F, et al. C2238 atrial natriuretic peptide molecular variant is associated with endothelial damage and dysfunction through natriuretic peptide receptor C signaling. *Circ Res.* 2013;**112**(10):1355-1364.
13. Jordan J, Birkenfeld AL, Melander O, Moro C. Natriuretic peptides in cardiovascular and metabolic crosstalk: implications for hypertension management. *Hypertension.* 2018;**72**(2):270-276.
14. Špiranec K, Chen W, Werner F, et al. Endothelial C-type natriuretic peptide acts on pericytes to regulate microcirculatory flow and blood pressure. *Circulation.* 2018;**138**(5):494-508.
15. Bubb KJ, Aubdool AA, Moyes AJ, et al. Endothelial C-type natriuretic peptide is a critical regulator of angiogenesis and vascular remodeling. *Circulation.* 2019;**139**(13):1612-1628.
16. Moyes AJ, Hobbs AJ. C-type natriuretic peptide: a multifaceted paracrine regulator in the heart and vasculature. *Int J Mol Sci.* 2019;**20**(9):2281.
17. Huntley BK, Sandberg SM, Heublein DM, Sangaralingham SJ, Burnett JC Jr, Ichiki T. Pro-B-type natriuretic peptide-1-108 processing and degradation in human heart failure. *Circ Heart Fail.* 2015;**8**(1):89-97.
18. Ibebuogu UN, Gladysheva IP, Houg AK, Reed GL. Decompensated heart failure is associated with reduced corin levels and decreased cleavage of pro-atrial natriuretic peptide. *Circ Heart Fail.* 2011;**4**(2):114-120.
19. von Lueder TG, Sangaralingham SJ, Wang BH, et al. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. *Circ Heart Fail.* 2013;**6**(3):594-605.
20. Díez J. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. *Eur J Heart Fail.* 2017;**19**(2):167-176.
21. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol.* 2013;**62**(4):263-271.
22. van Heerebeek L, Hamdani N, Falcão-Pires I, et al. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. *Circulation.* 2012;**126**(7):830-839.
23. Tarnow L, Gall MA, Hansen BV, Hovind P, Parving HH. Plasma N-terminal pro-B-type natriuretic peptide and mortality in type 2 diabetes. *Diabetologia.* 2006;**49**(10):2256-2262.
24. Kroon MH, van den Hurk K, Alsema M, et al. Prospective associations of B-type natriuretic peptide with markers of left ventricular function in individuals with and without type 2 diabetes: an 8-year follow-up of the Hoorn Study. *Diabetes Care.* 2012;**35**(12):2510-2514.
25. Waldo SW, Beede J, Isakson S, et al. Pro-B-type natriuretic peptide levels in acute decompensated heart failure. *J Am Coll Cardiol.* 2008;**51**(19):1874-1882.

26. Nakagawa Y, Nishikimi T, Kuwahara K, et al. MiR30-GALNT1/2 axis-mediated glycosylation contributes to the increased secretion of inactive human prohormone for brain natriuretic peptide (proBNP) from failing hearts. *J Am Heart Assoc.* 2017;**6**(2):e003601.
27. Liang F, O'Rear J, Schellenberger U, et al. Evidence for functional heterogeneity of circulating B-type natriuretic peptide. *J Am Coll Cardiol.* 2007;**49**(10):1071-1078.
28. Hammerer-Lercher A, Halfinger B, Sarg B, et al. Analysis of circulating forms of proBNP and NT-proBNP in patients with severe heart failure. *Clin Chem.* 2008;**54**(5):858-865.
29. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA.* 2017;**318**(8):713-720.
30. Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol.* 2013;**62**(15):1365-1372.
31. McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;**371**(11):993-1004.
32. Weder AB, Sekkarie MA, Takiyyuddin M, Schork NJ, Julius S. Antihypertensive and hypotensive effects of atrial natriuretic factor in men. *Hypertension.* 1987;**10**(6):582-589.
33. Fifer MA, Molina CR, Quiroz AC, et al. Hemodynamic and renal effects of atrial natriuretic peptide in congestive heart failure. *Am J Cardiol.* 1990;**65**(3):211-216.
34. Fonarow GC. B-type natriuretic peptide: spectrum of application. Nesiritide (recombinant BNP) for heart failure. *Heart Fail Rev.* 2003;**8**(4):321-325.
35. Boerrigter G, Burnett JC Jr. Recent advances in natriuretic peptides in congestive heart failure. *Expert Opin Investig Drugs.* 2004;**13**(6):643-652.
36. Chen HH, Glockner JF, Schirger JA, Cataliotti A, Redfield MM, Burnett JC Jr. Novel protein therapeutics for systolic heart failure: chronic subcutaneous B-type natriuretic peptide. *J Am Coll Cardiol.* 2012;**60**(22):2305-2312.
37. Wan SH, McKie PM, Schirger JA, et al. Chronic peptide therapy with B-type natriuretic peptide in patients with pre-clinical diastolic dysfunction (stage B heart failure). *JACC Heart Fail.* 2016;**4**(7):539-547.
38. Zakeri R, Burnett JC. Designer natriuretic peptides: a vision for the future of heart failure therapeutics. *Can J Physiol Pharmacol.* 2011;**89**(8):593-601.
39. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation.* 2005;**111**(12):1487-1491.
40. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA.* 2005;**293**(15):1900-1905.
41. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med.* 2011;**365**(1):32-43.
42. Chen HH, Anstrom KJ, Givertz MM, et al; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA.* 2013;**310**(23):2533-2543.
43. Soeki T, Kishimoto I, Okumura H, et al. C-type natriuretic peptide, a novel antifibrotic and antihypertrophic agent, prevents cardiac remodeling after myocardial infarction. *J Am Coll Cardiol.* 2005;**45**(4):608-616.
44. Moro C, Lafontan M. Natriuretic peptides and cGMP signaling control of energy homeostasis. *Am J Physiol Heart Circ Physiol.* 2013;**304**(3):H358-H368.
45. Bordicchia M, Liu D, Amri EZ, et al. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *J Clin Invest.* 2012;**122**(3):1022-1036.
46. Kim M, Platt MJ, Shibasaki T, et al. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med.* 2013;**19**(5):567-575.
47. Yamada-Goto N, Katsuura G, Ebihara K, et al. Intracerebroventricular administration of C-type natriuretic peptide suppresses food intake via activation of the melanocortin system in mice. *Diabetes.* 2013;**62**(5):1500-1504.
48. Magnusson M, Jujic A, Hedblad B, et al. Low plasma level of atrial natriuretic peptide predicts development of diabetes: the prospective Malmö Diet and Cancer study. *J Clin Endocrinol Metab.* 2012;**97**(2):638-645.
49. Polak J, Kotrc M, Wedellova Z, et al. Lipolytic effects of B-type natriuretic peptide 1-32 in adipose tissue of heart failure patients compared with healthy controls. *J Am Coll Cardiol.* 2011;**58**(11):1119-1125.

50. Christensen HM, Kistorp C, Schou M, et al. Prevalence of cachexia in chronic heart failure and characteristics of body composition and metabolic status. *Endocrine*. 2013;**43**(3):626-634.
51. Newton-Cheh C, Larson MG, Vasan RS, et al. Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. *Nat Genet*. 2009;**41**(3):348-353.
52. Arora P, Wu C, Khan AM, et al. Atrial natriuretic peptide is negatively regulated by microRNA-425. *J Clin Invest*. 2013;**123**(8):3378-3382.
53. Cannone V, Boerrigter G, Cataliotti A, et al. A genetic variant of the atrial natriuretic peptide gene is associated with cardiometabolic protection in the general community. *J Am Coll Cardiol*. 2011;**58**(6):629-636.
54. Jujic A, Nilsson PM, Engström G, Hedblad B, Melander O, Magnusson M. Atrial natriuretic peptide and type 2 diabetes development—biomarker and genotype association study. *PLoS One*. 2014;**9**(2):e89201.
55. Pfister R, Sharp S, Luben R, et al. Mendelian randomization study of B-type natriuretic peptide and type 2 diabetes: evidence of causal association from population studies. *PLoS Med*. 2011;**8**(10):e1001112.
56. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;**109**(5):594-600.
57. Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. *J Am Coll Cardiol*. 2006;**47**(1):85-90.
58. Miyashita K, Itoh H, Tsujimoto H, et al. Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. *Diabetes*. 2009;**58**(12):2880-2892.
59. Plante E, Menaouar A, Danalache BA, Broderick TL, Jankowski M, Gutkowska J. Treatment with brain natriuretic peptide prevents the development of cardiac dysfunction in obese diabetic db/db mice. *Diabetologia*. 2014;**57**(6):1257-1267.
60. Neeland IJ, Winders BR, Ayers CR, et al. Higher natriuretic peptide levels associate with a favorable adipose tissue distribution profile. *J Am Coll Cardiol*. 2013;**62**(8):752-760.
61. Lazo M, Young JH, Brancati FL, et al. NH2-terminal pro-brain natriuretic peptide and risk of diabetes. *Diabetes*. 2013;**62**(9):3189-3193.
62. Kjaer A, Appel J, Hildebrandt P, Petersen CL. Basal and exercise-induced neuroendocrine activation in patients with heart failure and in normal subjects. *Eur J Heart Fail*. 2004;**6**(1):29-39.
63. Dessì-Fulgheri P, Sarzani R, Serenelli M, et al. Low calorie diet enhances renal, hemodynamic, and humoral effects of exogenous atrial natriuretic peptide in obese hypertensives. *Hypertension*. 1999;**33**(2):658-662.
64. Bajaj NS, Gutiérrez OM, Arora G, et al. Racial differences in plasma levels of N-terminal pro-B-type natriuretic peptide and outcomes: the reasons for geographic and racial differences in stroke (REGARDS) study. *JAMA Cardiol*. 2018;**3**(1):11-17.
65. Wang TJ. Natriuretic peptide deficiency—when there is too little of a good thing. *JAMA Cardiol*. 2018;**3**(1):7-9.
66. Lam CS, Cheng S, Choong K, et al. Influence of sex and hormone status on circulating natriuretic peptides. *J Am Coll Cardiol*. 2011;**58**(6):618-626.
67. Birkenfeld AL, Budziarek P, Boschmann M, et al. Atrial natriuretic peptide induces postprandial lipid oxidation in humans. *Diabetes*. 2008;**57**(12):3199-3204.
68. Heinisch BB, Vila G, Resl M, et al. B-type natriuretic peptide (BNP) affects the initial response to intravenous glucose: a randomised placebo-controlled cross-over study in healthy men. *Diabetologia*. 2012;**55**(5):1400-1405.
69. Vila G, Grimm G, Resl M, et al. B-type natriuretic peptide modulates ghrelin, hunger, and satiety in healthy men. *Diabetes*. 2012;**61**(10):2592-2596.
70. Seferovic JP, Claggett B, Seidelmann SB, et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol*. 2017;**5**(5):333-340.
71. Meems LMG, Burnett JC Jr. Innovative therapeutics: designer natriuretic peptides. *JACC Basic Transl Sci*. 2016;**1**(7):557-567.