Natriuretic Peptides in Cardiovascular and Metabolic Crosstalk

Implications for Hypertension Management

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Natriuretic peptides are commonly considered cardiovascular and renal hormones. Indeed, genetic natriuretic peptide deletion promotes arterial hypertension and associated organ damage.[1] Conversely, pharmacological natriuretic peptide augmentation lowers blood pressure. Less recognized is the fact that natriuretic peptides potently affect lipid and glucose metabolism. Through these metabolic actions, natriuretic peptides may provide a pathophysiological link between cardiovascular and metabolic disease. Indeed, arterial hypertension and insulin resistance or overt type 2 diabetes mellitus commonly occur in the same patients. Similarly, heart failure is associated with impaired skeletal, muscular oxidative function and insulin resistance.[2,3] The review focusses on recent epidemiological, genetic, physiological, and pharmacological evidence linking the natriuretic peptide system with metabolic disease. Moreover, we discuss clinical trials evidence suggesting that natriuretic peptide modulation could be pursued further in metabolic disease prevention and treatment.

The Cardiac Natriuretic Peptide System

ANP (atrial natriuretic peptide) and BNP (B-type natriuretic peptide) are released from cardiac atria and ventricles, respectively. Both peptides are produced as preprohormones and are stored as prohormones in intracellular granules. The native peptides are released in equimolar amounts with N-terminal peptide fragments, which are more stable than the native hormones and can serve as natriuretic peptide release markers. Stretch of atrial or ventricular cardiomyocytes which can be secondary to increased sodium intake, physical exercise, or diseases associated with volume overload triggers natriuretic peptide release. Both natriuretic peptide and their N-terminal peptide fragments are clinically established heart failure biomarkers. Once released, natriuretic peptides raise renal sodium excretion, elicit vasodilation, and are the physiological antagonists of the renin-angiotensin system.[4] Natriuretic peptides also attenuate sympathetic nervous system activity at least in part through interaction with central vasopressin pathways.[5] ANP and BNP responses are primarily mediated by the GCA (guanylyl cyclase-coupled natriuretic peptide receptor; also known as NPR-A [natriuretic peptide receptor A]). NPR-C, which is sometimes referred to as scavenger receptor, is devoid of guanylyl cyclase activity and facilitates cellular natriuretic peptide uptake and degradation. In addition, natriuretic peptides are enzymatically cleaved by neprilysin. Neprilysin also degrades other peptides potentially modulating cardiovascular and metabolic regulation, such as bradykinin, endothelin-1, and glucagon-like peptide 1.

Epidemiological Association Between Natriuretic Peptides, Metabolic Risk, and Blood Pressure

In large-scale epidemiological studies, natriuretic peptide biomarkers showed strong associations with glucose metabolism and type 2 diabetes mellitus risk independently of established risk markers, including excess adiposity. In 3333 Framingham study participants without heart failure, plasma NT-proBNP and NT-proANP (N-terminal proANP and BNP) levels were inversely related to all components of the metabolic syndrome except for arterial hypertension.[6] Furthermore, natriuretic peptide levels were reduced in participants with insulin resistance indicated by an elevated homeostasis model assessment index.[6] Among 1274 participants of the KORA (Cooperative Health Research in the Augsburg Region) F4 cohort, the odds ratio for having central obesity, elevated triglycerides, the metabolic syndrome, impaired fasting glucose, or type 2 diabetes mellitus was substantially reduced in those with midregional (MR)-proANP plasma levels in the highest quartile.[7] Remarkably, MR-proANP increased together with blood pressure. Yet, circulating MR-proANP concentrations were inversely related to carotid intima-media thickness suggesting that metabolic and cardiovascular traits associated with MR-proANP may translate to structural vascular disease.[7]

The evidence on natriuretic peptide associations with glucose and lipid metabolism from cross-sectional surveys is strongly supported by longitudinal studies using incident type 2 diabetes mellitus as end point. In 1828 participants of the Malmo Diet and Cancer Study without diabetes mellitus at inclusion, reduced circulating MR-proANP concentrations heralded increased risk for type 2 diabetes mellitus after full

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adjustment for traditional risk factors.[8] The overall association was primarily explained by excess diabetes mellitus risk in participants in the lowest MR-proANP quartile.[8] Conversely, in a more recent analysis, circulating MR-proANP values in the high normal range were associated with lower prevalence of insulin resistance during follow up.[9] Among 7822 ARIC study (Atherosclerosis Risk in Communities) participants, NT-proBNP measurements at baseline were inversely related to risk for new-onset diabetes mellitus during a median follow-up of 12 years across sex, ethnicity, and obesity subgroups.[10] Others confirmed the association in older populations.[11] A smaller scale mechanistic study in lean healthy individuals suggests that the association between reduced natriuretic peptides and impaired metabolism is not explained by an effect of insulin resistance or perturbed glucose metabolism on cardiac natriuretic peptide release.[12]

Although reduced natriuretic peptide measurements are associated with incident and future metabolic risk, the state-of-affairs seems more complicated for blood pressure, as indicated above. Moreover, in normotensive blacks, elevated BNP measurements were associated with increased risk for longitudinal increases in blood pressure.[3] There are no data suggesting that natriuretic peptides could increase blood pressure. Instead, increased natriuretic peptide release seems to be a compensatory response attempting to restrain blood pressure.

Genetic Evidence Linking Natriuretic Peptide Deficiency With Metabolic Disease and Elevated Blood Pressure

Common variants in the genes encoding ANP and BNP precursors affect their circulating levels.[13] Alleles associated with increased natriuretic peptide concentrations were also associated with lower blood pressure and reduced odds of having arterial hypertension.[13] Recently, the micro RNA miR-425 was shown to negatively regulate ANP production, and a common genetic variant makes ANP production resistant to miR-425.[14] Post-translational modifications of proBNP seem to regulate BNP release.[15] Compared with whites, blacks exhibit 40% lower circulating NT-proBNP concentrations after adjustment for clinical covariates.[16] Genetic variations may contribute to ethnic differences in natriuretic peptide levels and susceptibility to cardiovascular and metabolic disease.

Among participants of the Malmo Diet and Cancer Study, 27 307 individuals were genotyped for the rs5068 variant of the gene encoding the ANP precursor, which is associated with increased circulating ANP concentrations. Carriers of at least 1 copy of the rs5068 G allele exhibited a lower likelihood of incident diabetes mellitus within 14-year follow up.[17] The association between rs5068 and a favorable metabolic profile was also shown in blacks.[18] In a study applying Mendelian randomization, the observed association between the rs198389 polymorphism and type 2 diabetes mellitus was compared with the expected association. The latter was computed from associations between NT-proBNP level and type 2 diabetes mellitus and NT-proBNP differences associated with the rs198389 C allele.[11] The analysis suggested a causal inverse relationship between BNP and type 2 diabetes mellitus.

Together, the epidemiological and genetic evidence strongly suggests that reduced availability of, both, ANP and BNP predisposes to insulin resistance, type 2 diabetes mellitus, and elevated blood pressure, whereas increased natriuretic peptide availability seems to be protective.

Relative Natriuretic Peptide Deficiency in Obesity

The tight association between excess adiposity and arterial hypertension, as well as type 2 diabetes mellitus may be explained in part by paradoxical natriuretic peptide deficiency. Given the increase in cardiac volume loading in obesity, one would expect to observe increased natriuretic peptide release. Instead, several large cohort studies reported inverse associations between circulating plasma natriuretic peptide levels, generally their N-terminal cleavage products and obesity.[19,20] Thus, adiposity seems to reduce natriuretic peptide availability through decreased release together with increased natriuretic peptide clearance. The latter may result in part from adipose NPR-C scavenger receptor upregulation in obesity, particularly, in individuals with concomitant arterial hypertension.[21,22] Finally, obesity may negatively affect natriuretic responses as indicated by reductions in GCA gene and protein expression in subcutaneous abdominal adipose tissue of obese subjects with and without type 2 diabetes mellitus[23–25] and in skeletal muscle.[26]

Physical Exercise and Weight Loss Augment Natriuretic Peptide Availability

Both physical exercise and weight loss are often recommended for cardiovascular and metabolic disease prevention. Some of the beneficial responses to these interventions may be mediated through increased natriuretic peptide availability and action. In healthy men, exercise on a bicycle ergometer acutely increased circulating ANP concentrations ≈2-fold with less pronounced changes in BNP concentrations.[27] Similar exercise-related responses have been observed in patients with heart failure or with obesity.[22,28] The response may be driven by increased venous return and cardiac filling pressure because exercise-induced ANP secretion is amplified by β-adrenoreceptor blockade.[29] Moreover, exercise during water immersion further augmented ANP release.[30] Exercise-mediated ANP release increases with exercise repetition.[31] A cohort study recently reported a positive correlation between physical activity level determined by triaxial accelerometry and plasma BNP concentrations.[32] Finally, in middle-aged obese individuals, GCA expression in human skeletal muscle was positively correlated with oxidative capacity and was upregulated through aerobic exercise training.[33]

The natriuretic peptide system has been assessed before and after weight loss in overweight and obese individuals experiencing modest weight loss through lifestyle interventions and massive weight loss through bariatric surgery. In overweight to obese individuals, weight loss through hypocaloric dieting during 6 months did not change the circulating MR-proANP concentrations suggesting that there was no major change in ANP release.[22] In other studies, multimodal interventions, including exercise and hypocaloric dieting substantially increased NT-proBNP and MR-proANP concentrations.[34–36]

We speculate that the addition of physical exercise to weight loss programs may be more effective in increasing natriuretic peptide release compared with interventions solely relying on caloric restriction. In any case, even modest weight loss is sufficient to reduce adipose NPR-C mRNA expression.[22,36] A reduction in natriuretic peptide clearance could conceivably increase natriuretic peptide availability even in the setting of unchanged release. In the event, modest weight loss through hypocaloric dieting enhanced the natriuretic and cGMP-response to ANP infusion in obese hypertensive human subjects.[37]

Several studies showed that substantial body weight reductions after bariatric surgery elicit a more robust increase in circulating NT-proBNP concentrations compared with the response observed with lifestyle interventions.[35,38]

Pharmacological Manipulation of Natriuretic Peptide Signaling

Recombinant ANP (Caperitide) and BNP (Nesiritide) have been developed for intravenous treatment of acutely decompensated heart failure. Nesiritide also ameliorated resistant arterial hypertension in a smaller scale study.[39] Their short plasma half-life and the need for intravenous or subcutaneous infusion preclude their chronic use. Therefore, newer designer natriuretic peptides that differ from the native peptides in terms of efficacy, specificity, and resistance to enzymatic degradation have been developed.[40] Another option to augment the system is to attenuate natriuretic peptide clearance. However, neprilysin is a promiscuous enzyme that in addition to natriuretic peptides degrades many other substrates. In particular, neprilysin interferes with the conversion of angiotensin I and II,[41] limiting the utility of neprilysin inhibition as monotherapy. Dual inhibition angiotensin of II subtype 1 receptor and neprilysin inhibition with sacubitril/valsartan decreases blood pressure more than angiotensin II subtype 1 receptor blockade alone.[42] The PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) showed improved survival in sacubitril/valsartan-treated patients with heart failure and reduced left ventricular ejection fraction compared with patients on enalapril.[43] PDE5 (phosphodiesterase 5) inhibition selectively blocks cGMP degradation, the second messenger of GCA and of soluble guanylyl cyclase, which is activated by nitric oxide. Thus, PDE5 inhibition does not selectively augment natriuretic peptide signaling. PDE5 inhibitors are currently approved for the treatment of pulmonary arterial hypertension and erectile dysfunction.

Natriuretic Peptide Influences on Cellular Metabolism

In the early 2000, we demonstrated a potent lipolytic effect of natriuretic peptides in human isolated adipocytes.[44,45] The response requires binding to GCA to activate a cGMP-dependent signaling pathway. Subsequently, cGK-Iα (cGMP-dependent protein kinase) is activated, which phosphorylates 1 rate-limiting enzyme of lipolysis, the hormone-sensitive lipase and perilipin.[46]

Natriuretic peptides induce a thermogenic program and uncoupling protein 1 in human mesenchymal-adipose–derived stem cells–derived adipocytes.[47] Activation of the p38 MAPK-ATF2 (mitogen-activated protein kinase–activating transcription factor-2) and PGC1α (peroxisome proliferator-activated receptor-gamma coactivator-1α) pathway through cGK-I seem to be involved.[47] The response requires mTORC1 (mammalian target of rapamycin complex 1) activation through direct Raptor Ser791 phosphorylation.[48] Natriuretic peptide signaling in adipocytes increases both oxygen consumption rate and mitochondrial oxidative gene expression. The process may involve AMP-activated protein kinase.[49] Finally, natriuretic peptides promote glucose uptake in human adipocytes in a cGMP-dependent manner, an effect which is blunted in adipocytes from obese individuals.[50]

Chronic treatment of human primary myotubes with natriuretic peptides upregulates PGC1α gene and protein expression, as well as mitochondrial oxidative genes and proteins, oxygen consumption, and fat oxidation.[33] Natriuretic peptide–treated human primary myotubes were protected from palmitate-induced lipotoxicity and insulin resistance.[26] However, no acute effect on glucose uptake in human skeletal muscle cells was observed.

Collectively, the literature suggests that natriuretic peptide signaling controls fatty acid mobilization from adipocytes, as well as mitochondrial biology and cellular energy metabolism in adipocytes and skeletal myocytes (Figure 1).

Metabolic Natriuretic Peptide Actions in Animal Models

Some natriuretic peptide actions related to lipid mobilization exhibit strong species specificity limiting the utility of animal models. Indeed, the relative resistance to the lipolytic effect of natriuretic peptides in adipocytes could be because of high NPR-C expression in certain species.[51] In mice, genetic NPR-C deletion restores a normal lipolytic response to ANP.[47] Full and adipose-specific NPR-C knockout mice featured reduced white fat pad mass concomitant with increased browning and UCP1 (uncoupling protein 1) protein expression.[47,52] Transgenic mice overexpressing BNP were partly protected from high-fat diet–induced weight gain and glucose intolerance. Elevated oxygen consumption and fat oxidation through increased muscular mitochondrial respiration were likely involved.[53] Ubiquitous cGK-I overexpression elicited a similar response.[53] BNP- and cGK-I-transgenic mice also exhibit a browning of white fat pads, thus rendering white adipocyte hypermetabolic with a thermogenic potential.

Preclinical studies with chronic treatment of mouse models for obesity and type-2 diabetes mellitus with natriuretic peptides have also been informative on their metabolic role and therapeutic potential. In obese diabetic db/db mice, 12 weeks of BNP infusion improved insulin and glucose tolerance.[54] BNP treatment reduced cardiac left ventricular mass and improved systolic function likely by ameliorating cardiac pressure overload and blood pressure. Cardiomyocyte apoptosis and cardiac fibrosis were also attenuated on BNP. We observed a remarkable effect of 4 weeks BNP treatment in obese and diabetic mice on blood glucose control and glucose tolerance. BNP treatment significantly reduced HbA1c (glycated hemoglobin A1c) levels and improved insulin sensitivity in obese diabetic db/db mice.[26] A similar response was observed in obese high-fat fed mice, in which BNP improved glucose tolerance and insulin sensitivity in skeletal muscle.

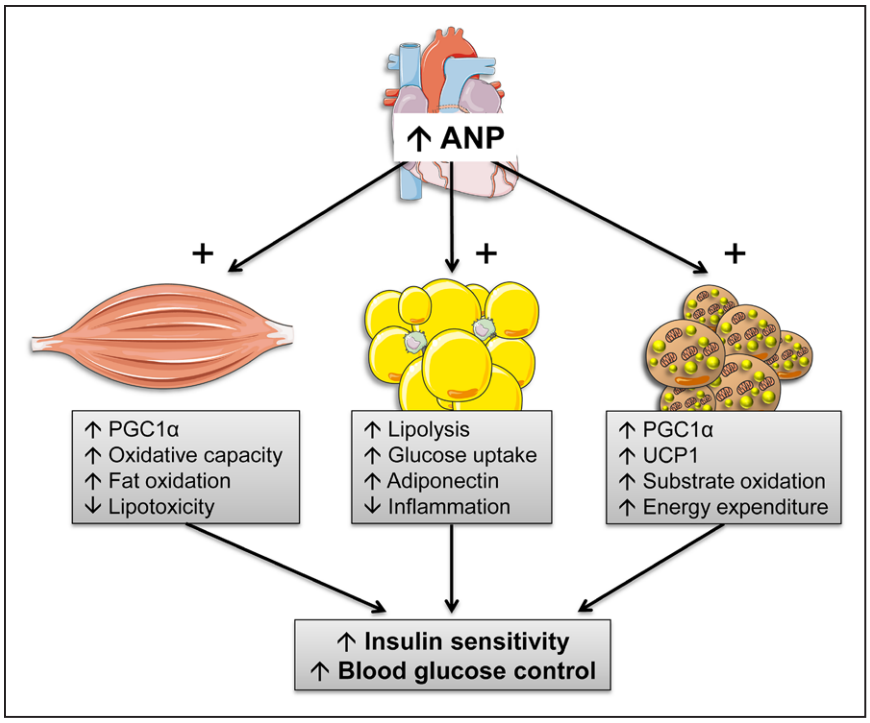

Figure 1. Integrative model of the various metabolic actions of ANP (atrial natriuretic peptide) in adipose tissue and in skeletal muscle. Interventions targeting the natriuretic peptide system through changes in natriuretic peptide and changes in natriuretic responsiveness. The figure uses the response of physical exercise as an example. Acute exercise increases ANP secretion, whereas chronic exercise upregulates ANP signaling in adipose tissue and in skeletal muscle. ANP induces fat oxidative capacity while ameliorating high-fat diet–mediated lipotoxicity in mouse skeletal muscle. In addition, ANP promotes lipolysis, browning, oxygen consumption, and glucose uptake in white and brown/beige adipocytes. All these biological effects collectively improve insulin and glucose metabolism. PGC1α indicates peroxisome proliferator-activated receptor-gamma coactivator-1α; and UCP, uncoupling protein.

Improved insulin signaling in skeletal muscle was paralleled by significant reductions in diacylglycerols and ceramides levels, as well as an upregulation of lipid oxidation rate.[26] We consistently noted reduced natriuretic peptide signaling, that is, reduced GCA expression and increased NPR-C expression, in adipose tissues and in skeletal muscle of obese and diabetic mice. NPR-C inhibition may be a promising therapeutic avenue in obesity and type-2 diabetes mellitus. Moreover, in one study, PDE5 inhibition in high-fat diet fed mice improved insulin sensitivity by enhancing insulin action in skeletal muscle,[55] whereas another study failed to confirm the effect even showing worsened glucose tolerance.[56] Increasing cGMP signaling through soluble guanylyl cyclase, which is engaged by nitric oxide rather than natriuretic peptides, protected from weight gain and ameliorated glucose metabolism.[57]

Remarkably, high-fat feeding led to reduction in the expression of GCA receptors in metabolic tissues together with NPR-C upregulation in adipose tissue without changes in circulating BNP concentrations.[26] The finding suggests that changes in natriuretic peptide signaling and, perhaps, reduced natriuretic peptide availability at the tissue level may precede systemic changes in natriuretic peptides.

Mechanistic Studies on Human Metabolism

Intravenous ANP infusion increases adipose tissue lipolysis and free fatty acid availability in a dose-dependent manner.[58–60] Lipolysis increases in adipose tissue but not in skeletal muscle.[59] Furthermore, short-term ANP infusion augmented lipid oxidation and postprandial energy expenditure in healthy men while decreasing blood pressure.[59,61] An increase in the ketone β-hydroxybutyrate suggested that hepatic lipid oxidation contributed to the response.[61] The latter may be particularly relevant in the setting of heart failure because the failing heart shifts substrate use to ketones[62] and metabolic natriuretic peptide actions may not desensitize in such patients.[63]

Natriuretic peptides modulate cytokine and adipokine responses and interfere with gut hormone secretion. For example, human BNP-32 infusion elicited ghrelin release while decreasing appetite.[64] ANP infusion has been shown to increase the circulating insulin-sensitizing adipokine adiponectin.[65] All these findings strongly suggest that the natriuretic peptide system has an important role in the crosstalk between cardiovascular and metabolic regulation in humans.[66]

Clinical Trials Evidence

Thus far, relatively few clinical trials assessed influences of natriuretic peptide manipulation on metabolic outcomes. A trial including obese patients with arterial hypertension tested the hypothesis that sacubitril/valsartan improves insulin sensitivity compared with the metabolically neutral comparator amlodipine. After 8-week treatment, sacubitril/valsartan, but not amlodipine, improved insulin sensitivity determined by hyperinsulinemic-euglycemic clamp.[67] Abdominal adipose tissue interstitial glycerol concentrations increased with sacubitril/valsartan, but decreased with amlodipine. Whole-body lipolysis and substrate oxidation did not change with either treatment.[67] The trial also assessed lipid metabolism during endurance exercise, which is potent stimulus for lipid mobilization. Exercise increased adipose tissue and systemic lipolysis. However, the response was not augmented on sacubitril/valsartan treatment.[68] The finding is in line with cellular studies suggesting that neprilysin in adipocytes does not control natriuretic peptide-mediated lipolysis.[69] Furthermore, sacubitril/valsartan treatment for 8 weeks did not alter the abdominal subcutaneous adipose tissue transcriptome and expression of proteins involved in lipolysis, natriuretic peptide signaling, and oxidative metabolism.[70] A post hoc analysis of PARADIGM-HF showed persistently lower hemoglobin A1c concentrations in patients treated with sacubitril/valsartan compared with patients on enalapril.[71] Insulin treatment was

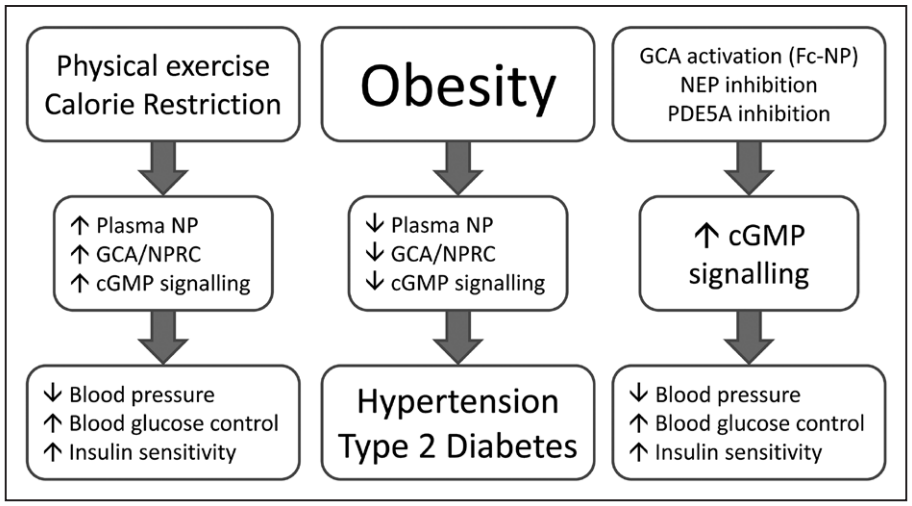

Figure 2. Working model linking natriuretic peptide deficiency to obesity-related hypertension and type 2 diabetes. Human and mouse data have linked obesity to NP (natriuretic peptide) deficiency, for example, reduced circulating levels and tissue signaling, which is causally involved in hypertension and type 2 diabetes development. Regular physical exercise and calorie restriction-mediated weight loss have been associated with enhanced circulating levels of natriuretic peptides and tissue signaling, which contributes to reduce blood pressure and improve blood glucose control. In the same line, pharmacological interventions targeting GCA (guanylyl cyclase-coupled natriuretic peptide receptor) activation through modified NP (Fc-NP), NEP (neprilysin) degrading NP, and PDE5A (phosphodiesterase-5A) degrading cGMP, can increase natriuretic peptide levels and tissue signaling, thus ameliorating arterial hypertension and type 2 diabetes risk. NPR-C indicates natriuretic peptide receptor C.

initiated in 7% of sacubitril/valsartan-treated patients and in 10% of the enalapril-treated patients. Similarly, fewer patients on sacubitril/valsartan required oral antidiabetic medications.

In a recent randomized placebo-controlled trial in overweight individuals with prediabetes, treatment with sildenafil 25 mg thrice daily improved whole-body insulin sensitivity assessed by hyperinsulinemic-euglycemic clamp.[72]

Potential Clinical Implications

Cardiovascular and metabolic diseases are tightly linked suggesting that there is a crosstalk between metabolic and cardiovascular organs. Epidemiology, genetics, mechanism-oriented investigations, and clinical trials suggest that cardiac natriuretic peptides are important in that regard. Decreased natriuretic peptide signaling predisposes to arterial hypertension and insulin resistance, which may progress to type 2 diabetes mellitus. Conversely, augmenting natriuretic peptide signaling lowers blood pressure, while improving oxidative metabolism and insulin sensitivity (Figure 2). The potential implications for patients with obesity and arterial hypertension, who are prone to relative natriuretic peptide deficiency are obvious. However, natriuretic peptide-mediated cardiometabolic crosstalk may also be relevant for other cardiovascular conditions. For example, heart failure is associated with abnormalities in skeletal muscle oxidative capacity[73] and insulin resistance.[2] It is tempting to speculate that natriuretic peptide-mediated improvements in metabolism could be beneficial in such patients. The idea that metabolism could be improved through increased natriuretic peptide availability in arterial hypertension and in heart failure, which are both associated with elevated natriuretic peptide release is counterintuitive. Perhaps, natriuretic peptide release while being increased is nevertheless insufficient to rescue metabolism. We speculate that there could be resistance to natriuretic peptide actions in peripheral tissues. Yet, natriuretic peptide-mediated lipolysis does not desensitize in patients with heart failure.[63] In any event, further increases in natriuretic peptides through neprilysin inhibition improved glucose metabolism in both conditions.[67,71] Natriuretic peptide availability and action can be affected through nonpharmacological measures, such as weight loss and physical exercise (Figure 2). Moreover, the system can be augmented through pharmacological approaches (Figure 2). We think that the potential of such drugs in addressing both, cardiovascular and associated metabolic disease deserves to be studied in more detail. However, pharmacological manipulation of natriuretic peptide signaling or other approaches affecting cGMP may not be without risks. For example, excess lipid mobilization could promote cachexia and worsen insulin sensitivity.

Disclosures

J. Jordan served as a consultant for Novartis, Boehringer-Ingelheim, Sanofi, Orexigen, Riemser, Vivus, and is cofounder of Eternygen GmbH. A.L. Birkenfeld received an unrestricted research grant from Novartis and is cofounder of Eternygen GmbH. The other authors report no conflicts.

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