



INTERACTING DISCIPLINES

Cardiac natriuretic peptides and obesity: perspectives from an endocrinologist and a cardiologist

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Abstract

Since their discovery in 1981, the cardiac natriuretic peptides (cNP) atrial natriuretic peptide (also referred to as atrial natriuretic factor) and brain natriuretic peptide have been well characterised in terms of their renal and cardiovascular actions. In addition, it has been shown that cNP plasma levels are strong predictors of cardiovascular events and mortality in populations with no apparent heart disease as well as in patients with established cardiac pathology. cNP secretion from the heart is increased by humoral and mechanical stimuli. The clinical significance of cNP plasma levels has been shown to differ in obese and non-obese subjects. Recent lines of evidence suggest important metabolic effects of the cNP system, which has been shown to activate lipolysis, enhance lipid oxidation and mitochondrial respiration. Clinically, these properties lead to browning of white adipose tissue and to increased muscular oxidative capacity. In human association studies in patients without heart disease higher cNP concentrations were observed in lean, insulin-sensitive subjects. Highly elevated cNP levels are generally observed in patients with systolic heart failure or high blood pressure, while obese and type-2 diabetics display reduced cNP levels. Together, these observations suggest that the cNP system plays a role in the pathophysiology of metabolic vascular disease. Understanding this role should help define novel principles in the treatment of cardiometabolic disease.

Key Words

- ▶ natriuretic peptides
- ▶ ANP
- ▶ ANF
- ▶ BNP
- ▶ NT-proBNP
- ▶ heart disease
- ▶ obesity

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Introduction

Two male patients with type 2 diabetes (T2D) and coronary heart disease had plasma levels of brain natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide (NT-proBNP) measured as part of routine evaluation. Both were hypertensive with hypercholesterolemia and

hypertriglyceridemia. Their glomerular filtration rate was normal (> 75 ml/min per 1.73 m²), HbA1c was $< 7\%$ with metformin, and C-reactive protein (CRP) was < 1 mg/dl in both. Patient A was 71 years old and had suffered an anterior myocardial infarction three years ago with



ST-segment elevation, which was initially treated with fibrinolytics and 24 h later using percutaneous coronary intervention with a drug eluting stent on the anterior coronary descending artery. He presented with a >70% stenosis on a diagonal artery, which was not treated and showed no significant stenosis in the remaining coronary arteries. His BMI was 34.8 kg/m², waist circumference 116 cm and was stable without chest pain in NYHA class I. The echocardiogram showed apical and lateral hypokinesia with left ventricular ejection fraction (LVEF) of 58%. Plasma BNP and NT-proBNP were 72 and 100 pg/ml, respectively (reference values for age and sex: BNP median 28 pg/ml (percentile 25–75th, 10–58 pg/ml); NT-proBNP median 45 pg/ml (percentile 5–95th, 14–140 pg/ml)).

Patient B, 58 years of age, had suffered a non-ST-elevation myocardial infarction two years earlier, and had received standard treatment. No coronary angiography was done due to his weight (144 kg). His BMI was 44.3 kg/m² and his waist circumference 137 cm. He was in stable condition without chest pain, in NYHA class II. The echocardiogram showed mild hypokinesia of the basal segment of the inferior wall and mild dilation of left ventricle with eccentric hypertrophy. LVEF was 66% and plasma BNP and NT-proBNP were 10 and <20 pg/ml, respectively (reference values for age and sex: BNP median 31 pg/ml, percentile 25–75th, 14–49 pg/ml; NT-proBNP median 25 pg/ml, percentile 5–95th, 5–88 pg/ml).

These findings posed the question as to why it is that in some patients the plasma levels of cardiac natriuretic peptides (cNP) are unexpectedly low, and what is their value in the prognosis for these patients?

The cardiologist's perspective

The cNP act as a basic functional link between cardiovascular system homeostasis, inflammation and certain metabolic functions (Fig. 1).

Increased secretion of cNP is a result of both mechanical and neurohumoral stimuli (1, 2). The main mechanical stimulus for the secretion of cNP is the increased pressure in the cardiac chambers leading to stretching of the myocardial fibers. This phenomenon is referred to as stretch-secretion coupling (3). Neurohumoral stimuli include endothelin-1, angiotensin II, adrenergic agonists and various cytokines (4). Increased left ventricular end-diastolic wall stress and left ventricular end-systolic wall stress correlate with an increase in plasma cNP in heart failure (5, 6). However, studies on cardiac transplant patients have shown that plasma cNP levels remain high even after intra-cardiac pressures

normalize following transplantation (7). During an acute cardiac allograft rejection episode, BNP – but not atrial natriuretic peptide (ANP) – plasma levels increase significantly above pre-rejection values independently of the surgical technique used (8). Plasma BNP levels during acute rejection episodes do not correlate with hemodynamic variables but correlate with the levels of regulated on activation, normal T expressed and secreted, insulin growth factor binding protein-1 and neutrophil activating protein-2 (4). In non-rejecting transplanted patients, despite the normalization of endothelin-1 plasma levels and diastolic and systolic functions, BNP remains high by comparison with control subjects (9).

Measuring cNP is useful as a diagnostic and prognostic tool (10, 11, 12). High plasma levels of cNP (e.g. BNP >63pg/ml or NT-proBNP >206 pg/ml) can quite precisely predict which patients are at risk for events such as hospitalization due to systolic heart failure or cardiovascular death (13, 14, 15, 16, 17, 18). Obese patients may have strikingly low levels of plasma cNP (19, 20, 21, 22) due to multiple mechanisms that might include increased neprilysin-neutral endopeptidase activity resulting in increased degradation of circulating cNP and increased adipose tissue expression of the NP clearance receptor C (NPRC). It has been proposed that suppression of proBNP₁₋₁₀₈ prohormone processing due to O-glycosylation at its cleavage site where furine or corin convertases act, prevents the formation of BNP₇₇₋₁₀₈ (functionally active) and NT-proBNP₁₋₇₆ (inactive) fragments, an event that is purportedly more frequent in diabetics and in insulin-resistant states (23, 24, 25). In heart failure patients, the precursor pro-hormone proBNP₁₋₁₀₈ is found circulating at lower than normal levels (26, 27).

Recently, the PARADIGM-HF trial showed that angiotensin receptor-neprilysin inhibition using the compound LCZ-696, 200 mg twice daily, compared with enalapril at 10 mg twice daily significantly reduced the risk of cardiovascular death and hospitalization in patients with heart failure with an LVEF ≤40%. However, death rates from cardiovascular causes were similar among diabetics compared with non-diabetics (28). Although this interesting finding could be an accidental one, other heart failure trials found that the benefit of this therapy in diabetics seems to be less than that in non-diabetics (29, 30, 31). This finding merits further research, since diabetics comprise 25–35% of the subjects in most studies (29, 30, 31, 32).

The obese are differentiated from the 'metabolically healthy obese' by an 'unhealthy metabolic' profile (33).

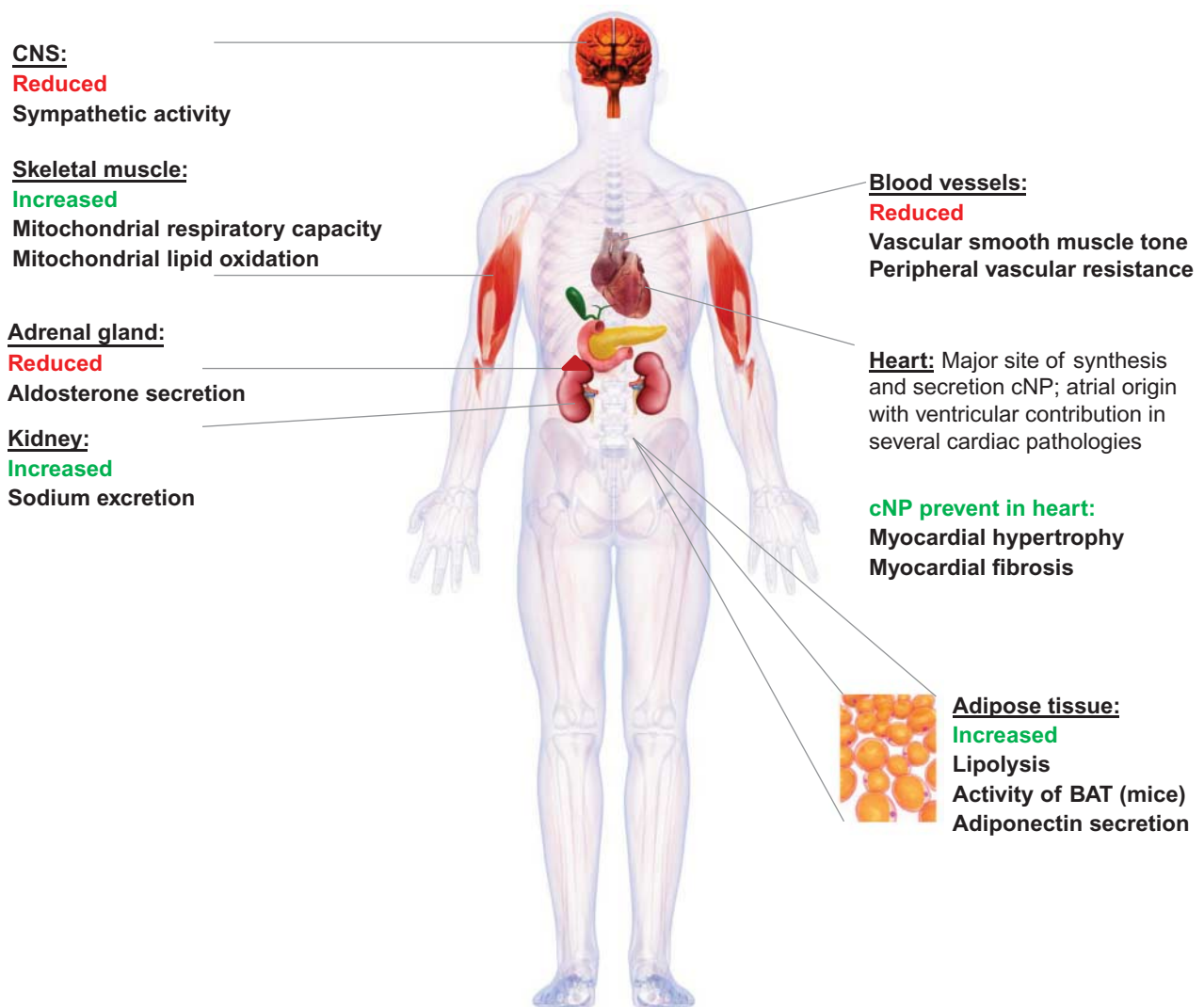


Figure 1
Main biological targets and effects of the cardiac natriuretic peptides ANP and BNP.

The latter is defined by increased waist circumference (>94 cm in men and >80 cm in women) or BMI ≥ 30 kg/m² accompanied by two or more of the following: hypertriglyceridemia (1.7 mmol/l), low HDL cholesterol (<1.03 mmol/l in men and <1.29 mmol/l in women), hyperglycemia (>11.1 mmol/l or a diagnosis of diabetes), hypertension ($\geq 130/85$ mmHg) or medication for high blood pressure (34, 35). In a 12-year follow-up of 61 299 subjects free from cardiovascular disease at baseline Mørkedal *et al.* (36) observed that systolic heart failure development was similar among 'metabolically healthy' compared to 'non-metabolically healthy' obese subjects, meaning that obesity *per se* creates a higher risk for developing systolic heart failure, especially if it is

long-lasting and severe (BMI >40 kg/m²). In contrast, the risk of acute myocardial infarction in 'obese metabolically unhealthy' subjects was significantly higher compared to 'obese metabolically healthy subjects' (35). Recently, it was reported that subjects with high plasma levels of NT-proBNP are at a greater risk of developing systolic heart failure whether they are obese or non-obese. However, unlike the non-obese who show a direct linear relationship between levels of NT-proBNP and systolic heart failure, the obese show a U-shaped relationship; i.e. those who have the lowest plasma levels are at just as much risk of developing systolic heart failure as those with the highest plasma levels (37). In contrast, the pathological weight loss caused by anorexia nervosa seems to be

related to high plasma levels of ANP (38). In severe obesity, bariatric surgery reduces the BMI and improves control of diabetes but it is not yet known if it reduces the risk of cardiovascular events (39, 40, 41, 42, 43, 44, 45, 46). In patients with severe obesity (BMI >40 kg/m²) before gastric bypass surgery, the median level of NT-proBNP was 54 pg/ml increasing by 125% after 1 year with no apparent relation to weight loss or glucometabolic parameters. It was speculated that an improvement in secretory cardiac function following surgery was responsible for the increase in circulating NT-proBNP (46).

Myocardial ischemia and cardiomyocyte stretch trigger the immediate release of cNP (47, 48) even when the LVEF is normal (49, 50). In a 9.2 year follow-up study of diabetic (about 7% of the cohort) and non-diabetic patients with chronic stable myocardial ischemia, high plasma levels of NT-proBNP were significantly associated with mortality regardless of left ventricular function (51). Recently, it was shown that in patients with stable coronary heart disease BNP and NT-proBNP were strong predictors of long-term (6.5 ± 3.3 years) cardiovascular events and notably, when NT-proBNP was added to the clinical predictors, it performed better than BNP in risk classification for adverse cardiovascular events (52). Serial measurement data for NT-proBNP in patients with chronic stable angina have shown a wide intra-individual variation. An increase by >42% or a decrease by >30% relative to baseline values is required to indicate a significant change (53, 54). In patients presenting with acute chest pain, cNP plasma levels help the diagnosis and prognosis when used together with a non-diagnostic ECG and a negative troponin. cNP measured in these patients at rest predict future cardiac events at 30 and 180 days and at 1 year (55, 56, 57, 58). If myocardial ischemia is evident during the stress test, an elevation of the plasma levels of NT-proBNP detects ischemia and predicts cardiovascular events (59). Likewise, in non-ST-elevation acute coronary syndromes, cNP add prognostic information to the clinical indicators (60, 61, 62, 63) (Table 1).

In a recent investigation (62), BNP was shown to be an independent predictor of mortality on entering the study. At 1 year of follow-up BNP plasma levels provided added value over the TIMI and GRACE scores. cNP are stronger predictors of mortality than troponin in patients that will eventually develop myocardial infarction. In ST-segment-elevation acute coronary syndromes cNP plasma levels also add prognostic information independently of the LVEF (50, 64, 65) and in addition, predict which patients with primary percutaneous coronary

intervention (PCI) may be discharged earlier thus saving health resources (66).

It has been shown experimentally that ANP is associated with salt-sensitive high blood pressure (67). In humans it has been shown that plasma ANP and high blood pressure correlate negatively. Alleles associated with the highest levels of NP were also associated with a lower risk of high blood pressure (68, 69). In keeping with these findings, another study showed a relative deficiency of cNP at all the different stages of high blood pressure in humans consisting of low levels of proBNP₁₋₁₀₈ and ANP₉₉₋₁₂₆. Low plasma levels of BNP₇₆₋₁₀₈ and NT-proBNP₁₋₇₆ were observed in the first hypertensive stages together with a reduction of NT-ANP₁₋₉₈ in stage I (70).

A possible therapeutic modality to supplement cNP in those cases in which circulating cNP are deemed deficient (like in hypertension or heart failure) is suggested by the development of a recombinant human serum albumin-atrial natriuretic factor (ANF) (71) molecule. This compound, when injected into mice increased circulating cGMP and decreased blood pressure demonstrated a half-life of >80 min, which is considerably longer than the 5–10 min half-life for native ANF (71, 72, 73).

From the preceding, it may be surmised that elevated cNP levels are strong markers of future cardiovascular events, especially cardiovascular death. On the other hand, cNP plasma levels lower than expected in obese and diabetic patients could be predictive of adverse outcomes.

In summary, the two patients discussed above had similar metabolic profiles, LVEF >50% but a different BMI and cNP profile. Patient A was not severely obese and had slight residual myocardial ischemia with BNP and NT-proBNP within low to moderate values expected for systolic heart failure and cardiovascular mortality on follow-up. Patient B suffered from severe obesity, with very low plasma levels of cNP with a prognosis related to his BMI of >40 kg/m² and probably also to a deficit of cNP, placing him in the high-risk category for developing systolic heart failure and eventual cardiovascular death.

The endocrinologist's perspective

Our patient A has markedly higher BNP and NT-proBNP levels compared to patient B. This can largely be explained by the better ejection fraction of patient B, but there might also be other contributing factors. For example, recent studies suggest an inverse relationship between circulating cNP levels and bodyweight as well as with insulin resistance and T2D (19, 74, 75, 76, 77, 78) (Table 1). This

Table 1 Values for cardiac natriuretic peptide plasma levels in heart failure and coronary heart disease.

Clinical syndrome	Natriuretic peptide (pg/ml)	Value	Reference
Acute heart failure (exclusion cut-off point)	BNP	<100	(11, 133)
Non-acute presentation of possible heart failure (exclusion cut-off point)	NT-proBNP	<300	(11)
	BNP	<35	
Chronic heart failure (indicators of high risk)	NT-proBNP	<125	(134)
	BNP	>125	
Unstable angina (indicators for non-invasive stress testing)	NT-proBNP	>1000	(135)
	BNP	<80	
Stable chronic coronary disease (cardiovascular death %)	NT-proBNP	<250	(51)
		BNP	
		Q II 18–42 (10)	
		Q III 43–102 (15)	
		Q IV >102 (28)	
		Q I <74 (4)	
	NT-proBNP	Q II 74–174 (9)	
		Q III 175–460 (17)	
		Q IV >460 (30)	

Q, quartile.

correlation can also be observed in patients with congestive heart failure, despite increased cNP levels, due to cardiac wall stress (79). Several explanations have been proposed. First, increased cNP degradation seems to be one possible cause. cNP are cleared and degraded by neutral endopeptidase neprilysin and natriuretic peptide receptor C (NPRC) (80, 81). Natriuretic peptide receptor A (NPRA) and NPRC have been identified in human adipose tissue in abundance, implying that adipose tissue sustains a regulatory function on the NP system (82, 83, 84). Interestingly, compared to non-obese and normotensive individuals, NPRC is increased in adipose tissue of obese hypertensive patients (85). Insulin has been observed to induce NPRC expression in human adipocytes (84) and monocytes (83), and might, hence, link conditions associated with hyperinsulinemia (e.g. obesity and insulin resistance), to a relative NP deficit. Additionally, neprilysin, the NP degrading endopeptidase, is expressed at increased levels in obesity (86). These data argue for obesity and insulin resistance being conditions in which cNP are degraded at an accelerated pace. Second, very recent experimental data also suggest that myocardial BNP expression is markedly decreased in mice fed a high fat diet (87), an observation that warrants clinical confirmation.

A cNP deficit in patients with components of the metabolic syndrome might be of clinical relevance. First, it might link obesity to arterial hypertension. Obese individuals have a higher prevalence of arterial

hypertension compared to lean subjects (88). Although obesity-related arterial hypertension has been intensively studied, not all mechanisms are well understood (89, 90). By reduced vasodilatory and sodium-excretion activity, as well as decreased suppression of the renin–angiotensin–aldosterone-system (RAAS), a cNP deficit might contribute to obesity related hypertension. Interestingly, in lean subjects, application of a sodium load induces myocardial cNP secretion and stimulates natriuresis (91, 92, 93, 94), a response which is blunted in patients with obesity (95). Together, these data argue that obesity promotes hypertension partly through reduced vascular and renal NP responses as well as through impaired NP-mediated RAAS inhibition. Second, cNP also have beneficial actions on cardiac remodelling in essential hypertension, reducing left ventricular hypertrophy (96). Conversely, conditions with a cNP deficit are associated with cardiac hypertrophy in hypertensive patients. In this regard, hypertensive patients with the metabolic syndrome present with lower ANP and NT-proBNP levels and increased left ventricular mass compared to hypertensive patients without the metabolic syndrome and insulin resistance (97).

Finally, the cNP deficit in patients with the metabolic syndrome might be part of a vicious circle which maintains metabolic disease. cNP have distinct metabolic effects. For instance, cNP exert lipolytic properties mediated by a cGMP-dependent protein kinase G activating pathway. cGMP-activated protein kinase G (GK-I) activates perilipin A and hormone sensitive lipase

mediated triglyceride hydrolysis (98, 99, 100, 101). Interestingly, these effects seem not to interact with the lipolytic effects of catecholamines (99, 102) and the effect seems to be independent of the regulation of insulin (103).

Besides a direct activating effect on lipolysis and lipid oxidation, cNP also control secretion of the insulin sensitizing adipokine adiponectin. In humans, ANP acutely increases systemic levels of total and high molecular weight adiponectin (104). These findings are in line with some observational studies showing positive associations between systemic cNP and adiponectin concentrations, as for example in heart failure patients (105, 106). This finding might also explain the ‘adiponectin paradox’ in patients with congestive heart failure.

cNP also exert other relevant metabolic actions on adipose tissue. Treating a human derived adipose cell line with ANP results in the uncoupling of cellular respiration (107) as well as ‘browning’ of white adipose tissue. The response seems to be mediated by p38 MAP kinase, which increases uncoupling protein 1 (UCP1) transcription (107). Upon cold exposure, systemic NP concentrations increase and NPRC expression in adipose tissue decreases. Similarly, forced PKG expression in primary adipocytes leads to an increase in UCP1 expression and activates a thermogenic program. Together, these studies suggest that the NP system induces a ‘browning’ program in adipose tissue (108).

cNP also exert metabolic actions in liver and skeletal muscle. We observed that short term i.v. administration of ANP acutely increases lipid oxidation (102, 109) and postprandial energy expenditure in healthy individuals (110). Circulating β -hydroxybutyrate increases, indicating enhanced hepatic lipid oxidation. Apart from acute effects on lipid oxidation (110), ANP and BNP induce skeletal muscle mitochondrial biogenesis, respiration and lipid oxidation in human cells and in rodents, *in vitro* and *in vivo* (111, 112). Chronic overexpression of BNP and GK-I each led to increased muscle mitochondrial content, oxidative capacity and lipid oxidation in rodents (111). Enhanced oxidative metabolism is associated with protection from diet induced obesity and insulin resistance (113). Heterozygous NPRC knockout mice are prone to gaining weight and become insulin resistant (111). The mechanism linking NP signalling to mitochondrial biogenesis and lipid oxidation in skeletal muscle includes activation of the co-transcriptional activator peroxisome proliferator-activated receptor γ coactivator (PGC)-1 α and peroxisome proliferator-activated receptor- δ , both of which are important factors of mitochondrial biogenesis in skeletal muscle (111).

In human myotubes, we observed that cNP stimulate PGC-1 α , maximal mitochondrial respiratory capacity and lipid oxidation (112). Moreover, NPRC expression positively correlates with PGC-1 α expression in the skeletal muscle of individuals after a chronic physical training program. Similarly, cell culture studies show that cGMP restores glucose and insulin induced mitochondrial dysfunction in cultured C2C12 myotubes (114), nitric oxide signalling via cGMP mediates activation of PGC-1 α , and mitochondrial biogenesis in various murine tissues (115).

Hepatic and skeletal muscle lipid content has been associated with insulin resistance (113). In liver and skeletal muscle, insulin resistance develops when bioactive lipid species accumulate, such as intracellular diacylglycerol (113). In obesity and the metabolic syndrome, this lipid accumulation is primarily due to excessive caloric intake that exceeds the capacity of hepatocytes and myocytes to metabolize or export fatty acids, while refining mitochondrial respiration and enhancing lipid oxidation have been proved to improve lipid utilization and insulin sensitivity (116, 117, 118). So far, there is no evidence that cNP directly interact with the insulin signalling cascade (109, 119). It is tempting to speculate that cNP could ameliorate lipid-induced insulin resistance through improvements in hepatic (110) and muscular (112) lipid oxidation. In line with this notion, cNP preserves mitochondrial function and insulin sensitivity in high fat diet mice (111). Cross sectional studies support the hypothesis that cNP protect from the development of obesity and T2D in patients (78, 120, 121, 122). Conversely, data from the Framingham Heart Study and the Malmö Diet and Cancer study show that reduced cNP concentrations correlate with a higher probability of insulin resistance in lean and obese individuals (76). Moreover, in the latter study low cNP concentrations are predictive of new-onset diabetes (123). Together, these data suggest that a cNP deficit, as observed in obese patients with the metabolic syndrome, contributes and aggravates metabolic vascular disease, and thus, prognosis. Further studies are needed to determine how such a deficit can be corrected. Life style interventions as well as pharmacological approaches might be of benefit in this regard (28, 124). While physical activity increases cNP levels acutely and augments NPRC expression in skeletal muscle cells (112), physical activity coupled with a low calorie diet seems to increase cNP levels chronically (125); an observation that seems to depend on the amount of weight loss (126, 127). Experimental data further suggests that the incretin glucagon like peptide 1 (GLP1) might be of relevance in the regulation of NP secretion. The GLP1

receptor agonist liraglutide, which is widely used for the treatment of T2D, has been shown to induce cardiac ANP release in mice, leading to enhanced natriuresis and vasodilatation (128) without inducing congestive heart failure. So far 25 clinical studies failed to demonstrate a similar effect of liraglutide when administered acutely (129) or sub-chronically to patients (130). Chronic liraglutide treatment, accompanied by weight loss, however, seems to increase circulating ANP as well as BNP concentrations in diabetic patients (131). Clearly, future studies need to address the important question how a cNP deficit in obesity and T2D can be reversed most efficiently (132).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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