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Review

Natriuretic peptide control of energy balance and glucose homeostasis

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ABSTRACT

Cardiac natriuretic peptides (NP) have recently emerged as metabolic hormones. Physiological stimulation of cardiac NP release as during exercise may contribute to increase fatty acid mobilization from adipose tissue and their oxidation by skeletal muscles. Clinical studies have shown that although very high plasma NP level characterizes cardiac dysfunction and heart failure, a consistently reduced plasma NP level is observed in metabolic diseases such as obesity and type 2 diabetes. A low circulating NP level also predicts the risk of new onset type 2 diabetes. It is unclear at this stage if the "natriuretic handicap" observed in obesity is causally associated with the incidence of type 2 diabetes. Recent work indicates that NP can activate a thermogenic program in brown and white fat, increase energy expenditure and inhibit food intake. Mouse studies also argue for a key role of NP in the regulation of energy balance and glucose homeostasis. This review will focus on recent human and mouse studies to highlight the metabolic roles of NP and their potential relevance in the context of obesity and type 2 diabetes.

1. Introduction

Atrial natriuretic peptide (ANP) was discovered and isolated from rat atrial extracts about three decades ago as « a novel heart peptide with potent diuretic and natriuretic properties » [1]. Brain NP (BNP) and C-type NP (CNP) were later identified as other members of this family of hormones. ANP and BNP secretion by the heart illustrated for the first time the endocrine role of the heart in the control of sodium and water homeostasis.

During the last decade, NP have emerged as metabolic hormones (Fig. 1). Pioneer studies reported a potent lipolytic role in human fat cells as previously discussed [2,3]. More recent work illustrates that NP control not only fat mobilization, but also fat utilization by promoting energy dissipation as heat in brown adipose tissue (BAT) [4], facilitating the browning process of white adipose tissue (WAT) [4] as well as fat oxidation in skeletal muscle [5]. It was also shown that NP can target the liver, the pancreas, the gut and the central nervous system to influence metabolic regulation. In parallel, numerous epidemiological and cohort studies reported a negative association between plasma NP levels and obesity [6], hypertension [7], insulin sensitivity [8,9] and type 2 diabetes (T2D) [10,11]. Prospective studies further highlight the predictive value of plasma NP levels in the development of new onset T2D [10].

Together human epidemiological and mouse studies argue for a pivotal role of cardiac NP in the regulation of energy metabolism. The purpose of this review is to give an updated overview of the various metabolic actions of NP reported in humans and mouse models, and their potential contribution to obesity and T2D.

2. Physiology of NP

2.1. Secretion

2.1.1. At rest

The NP family is characterized by a ring structure of 17 amino acids closed by an intra-molecular disulfide bridge. The ring structure allows NP to bind and activate their receptors. ANP and BNP are mainly produced in right atrial cardiomyocytes in standard physiological condition [12]. They are synthesized as preprohormones, stored as prohormones in atrial secretory granules, and secreted in response to mechanical stretch of cardiomyocytes [13]. Furin and corin are two cardiac proteases responsible for the processing of proNP in mature forms and enable their release into the circulation with the N-terminal fragment [14]. In standard physiological conditions, a negligible amount of proBNP crosses atrial wall, while

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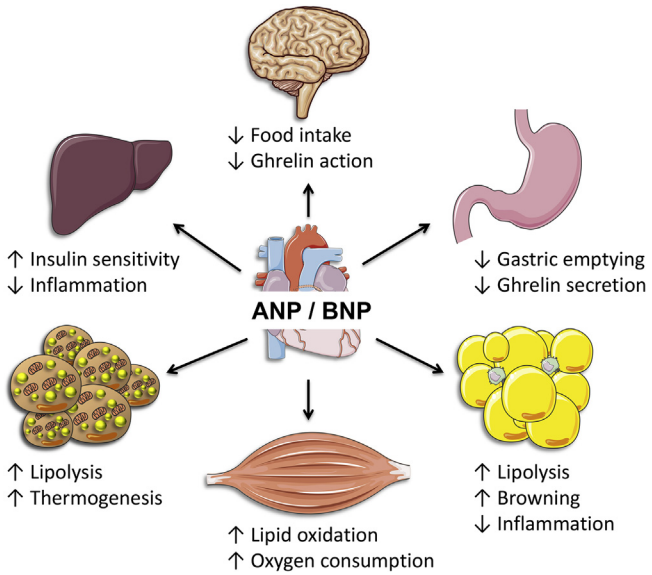

Fig. 1. Current model of the various metabolic actions of natriuretic peptides in the control of energy metabolism and glucose homeostasis.

proBNP expression and secretion is robustly induced in hypertrophied ventricles of failing hearts. This observation was at the basis of using N-terminal proBNP (NT-proBNP) as a diagnostic and prognostic factor in heart failure (HF) [15].

Besides mechanical stretch, NP secretion is regulated by circulating hormones. Recently, Kim et al. demonstrated the presence of GLP1 receptors on right atrial cardiomyocytes and that their stimulation, by a GLP1 receptor agonist liraglutide, induce a 1.8 fold increase in ANP secretion *via* an Epac2 pathway [16]. Thus at least in mice, the blood pressure lowering effect of GLP1R agonists appears mediated by ANP. Interestingly weight loss observed after 12 weeks of liraglutide treatment in T2D obese patients is significantly correlated with elevated plasma ANP and BNP levels [17]. However, recent human studies investigating the hemodynamic effects of GLP1 infusion could not reproduce mouse data and confirm the existence of a gut–heart axis in healthy males [18] and in obese T2D with hypertension [19].

2.1.2. During exercise

Acute exercise increases cardiac output and enhances ANP secretion. Acute exercise on bicycle ergometer increases plasma ANP levels by about 2-fold while plasma BNP levels are only marginally increased (30%) at the highest workload (175 W) [20]. Several studies reported an elevated ANP secretion during exercise [21,22], while this remains more controversial for BNP [23,24]. This appears mainly driven by increased venous return and cardiac filling pressure since exercise-induced ANP secretion is amplified by prior administration of a β-blocker [25]. Another study reported a positive association between plasma BNP levels and physical activity levels [26].

2.2. Receptors and biological roles

ANP and BNP exert their main biological actions through the binding to a membrane-bound specific guanylyl cyclase receptor called NP receptor-A (NPRA or GC-A). On the other hand, CNP preferentially binds with high affinity to another receptor called NPRB or GC-B. NP binding to an NPRA homodimer enables the activation of guanylyl cyclase and subsequent hydrolysis of GTP into the second messenger cGMP. Elevated levels of cGMP elicit the various biological responses through cGMP-regulated ion-channels, cGMP-dependent protein kinases (cGK), and possibly other effectors' protein [27]. NPRA is widely distributed throughout the cardiovascular system, as well as in several metabolic organs such as adipose tissues (AT), skeletal muscle, liver, brain, pancreas, and gut. NPRA expression is negatively regulated by NP, angiotensin II, endothelin I, TGF-β while vitamin D, glucocorticoids and osmotic stimuli are thought to increase NPRA transcription [12]. Through the specific binding to NPRA, ANP and BNP mediate numerous biological responses with the aim to lower blood volume and pressure as previously reviewed in detail elsewhere [12,13,28]. This includes a shift of intravascular fluid into the interstitial space, suppression of the renin–angiotensin–aldosterone system, and inhibition of plasma renin activity, of the sympathetic nervous system, and of aldosterone secretion, to reduce extracellular volume and facilitate natriuresis.

2.3. Degradation/clearance

NP are quickly removed out of the bloodstream by different processes: they can be internalized by their specific receptor NPRC, degraded by extracellular proteases such as neprilysin (NEP), dipeptidyl peptidase 4 (DPPIV), and insulin degrading enzyme (IDE), or secreted into body fluids like urine and bile. ANP half-life is about 2 min in human and 10 times lower than those of BNP. This difference can be partly explained by the N-terminal BNP asymmetry that lowers its affinity for NPRA and NPRC. NP are preferentially cleared in lungs, liver and kidneys [13].

2.3.1. NPRC

NPRC has an extracellular domain that is 30% homologous to those of NPRA and enables NP binding, however it is not coupled to a GC activity so NPRC scavenges, internalizes and induces the degradation of bound NP. NPRC is the most widely expressed NPR. NPRC is largely expressed in the cardiovascular system, lungs and AT. The tissue concentration of NPRC regulates the availability of NP and so their local action at the cell membrane. The disappearance of a bolus injection of [^{125}I]ANP is two-third longer in mice lacking NPRC compared to WT mice, which is accompanied by a significantly lower blood pressure [29]. NPRC expression is inhibited by NP, vasopressive hormones such as angiotensin II, endothelin I, arginine vasopressine, growth factors, and salt intake. Inversely, TGF-β, vitamin D and chronic HF up-regulate NPRC expression [30,31]. NPRC sequences revealed an A/C polymorphism in a conserved promoter/enhancer region in humans. In overweight and obesity, the homozygous C/C hypertensive subjects had significantly lower plasma ANP compared with A/C patients suggesting an increased NPRC-mediated ANP clearance in homozygous C/C patients [32]. Moreover male subjects from the Olivetti Heart Study in Naples carrying the A(-55)A NPRC genotype had a significantly lower prevalence of overweight, obesity, and abdominal adiposity [33].

Interestingly NPRC and NPRA seem to be regulated in opposite directions in metabolic organs. In 1997, Sarzani and coworkers observed that fasting dramatically lowers NPRC mRNA in WAT and BAT from rats without modification in renal cortex [34], while its expression highly increases under high fat feeding in mouse skeletal muscle, WAT and BAT [35]. In contrast to NPRA, 3T3-L1 adipocytes exposed to insulin greatly increase their NPRC expression through a PI3K pathway [36]. In humans, NPRC gene expression in subcutaneous AT and visceral AT strongly correlated with fasting insulin levels. Thus NPRC mRNA levels in AT are induced upon a euglycemic hyperinsulinemic clamp [37]. Surprisingly, insulin also significantly enhances NPRC expression in

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blood monocyte, making a potential site for NP clearance in systemic bloodstream.

2.3.2. Endopeptidases

2.3.2.1. Neutral endopeptidase. NEP, also known as neutral endopeptidase, enkephalinase, CD10, common acute lymphoblastic leukemia antigen (CALLA), is widely expressed at the cell surface of numerous cell types. NEP is highly expressed in the brush border of kidney and small intestine and AT, although substantial NEP levels are also found in the brain, salivary glands, islets of Langerhans, gut wall, nasal mucosa and lung [38]. This enzyme cleaves vasoactive peptides such as neuropeptides, endothelin I, angiotensin II and mature NP by hydrolyzing bonds of hydrophobic residues [39]. NEP has also been shown to be secreted in certain physiological fluids such as plasma, cerebrospinal fluid, amniotic fluid and seminal plasma [40]. The ectodomain contains five putative N-glycosylation sites that regulate transport and activity of the enzyme to the cell surface. Exposure to high glucose concentrations (40 mM) and/or high fatty acid concentrations (40 μM) maximally stimulates NEP activity in human endothelial cells by increasing glycation and lipid peroxidation that is reversible when these cells are treated with vitamin C or E [39]. The up-regulation of NEP activity appears independent of changes in NEP transcription or translation [41]. Moreover plasma NEP activity is associated with metabolic syndrome, insulin resistance and cardiovascular risk factors in human subjects [42].

As for NPRC, NT-proBNP and mid regional-proANP (MR-proANP) are refractory to enzymatic cleavage by NEP. Of importance, pharmacological inhibition of NEP by Candoxatril does not cause clinically meaningful reduction in blood pressure despite slightly elevated plasma ANP levels, possibly because of NEP-dependent breakdown of other vasoactive polypeptides such as angiotensin II and endothelin I [43]. In addition, a combined pharmacological inhibition of NEP and angiotensin II receptor-2 (AT2) by the dual-acting drug LCZ696, provides an additional reduction of blood pressure compared to the AT2 blocker valsartan alone [44].

2.3.2.2. Others. Circulating NP can also be inactivated by the dipeptidyl peptidase-IV (DPPIV or CD26) that cleaves the N-terminal peptide. Inhibition of this enzyme is chiefly studied to enhance the half-life of incretin hormones such as glucagon-like peptide-1 (GLP1) that improve blood glucose control. However DPPIV cleaves mature BNP (1–32) *in vitro* into BNP (3–32) which display a reduced biological activity [45]. Although DPPIV does not directly target ANP, it has been shown that cardiac ANP expression is greatly enhanced in DPPIV knockout mice [46]. This could be partly due to the higher half-life of GLP1 that can stimulate ANP secretion in the right atria of the heart [16]. Further studies are needed to better discriminate the importance of DPPIV on the systemic and/or local concentrations of NP and their biological activity in target tissues.

The insulin degrading enzyme (IDE), an ubiquitous zinc metalloprotease found in cytoplasmic and membrane fraction of several cell types, has also been shown to enzymatically cleave NP *in vitro* with a higher affinity for ANP [47]. Thus some of the beneficial effects of inhibiting IDE could involve changes in plasma NP levels [48].

2.4. Association with cardiovascular diseases

As discussed earlier, NT-proBNP is widely used in the clinic as a diagnostic tool of acute and/or congestive HF [15]. BNP expression and secretion are strongly induced as a function of left ventricular hypertrophy [49]. BNP plasma levels strongly increase in patients with HF and positively correlate with the severity of HF according to the New York Heart Association classification system [50]. Elevated plasma BNP levels after optimized treatment in patients with congestive HF also predict a higher risk of morbidity and mortality [51,52].

Besides the sympathetic nervous and the renin–angiotensin–aldosterone systems [53], the NP system has been extensively studied to unravel the pathophysiological link between hypertension, obesity and the metabolic syndrome. It was proposed that obese individuals have an impaired NP response defined as a “natriuretic handicap”. In obese hypertensive subjects, plasma ANP levels are significantly lower than in obese normotensive subjects despite a similar left ventricular mass [7]. Interestingly, plasma NP levels remain significantly reduced in obese compared to lean individuals with heart failure [54]. Thus suggesting that the “natriuretic handicap” emerges during obesity.

2.5. Association with obesity and type 2 diabetes

The “natriuretic handicap” hypothesis was later supported by the observation of a strong inverse relationship between plasma BNP levels and body mass index (BMI) in the Framingham Heart Study [6]. This occurs despite a higher left-ventricular mass and end-diastolic pressure in obese compared to lean people [55]. In a prospective study with a 16 year follow-up, low plasma level of MR-proANP at baseline were associated with longitudinal changes in fasting blood glucose and new onset T2D [10]. A summary of main human clinical studies providing a link between metabolic diseases and NP levels is provided in Table 1.

The link between plasma NP levels and metabolic diseases was confirmed in another study, where the A/G single nucleotide polymorphism of the ANP gene was associated with elevated NT-proANP plasma levels and reduced systolic blood pressure (SBP), BMI, waist circumference, and a lower risk of metabolic syndrome compared to A/A carriers [56]. This observation was later substantiated by a 14-year follow-up study where A/G carriers had lower incident T2D even after multiple adjustments for age, sex and BMI [57].

3. Metabolic roles of NP

Over the last decade, several papers highlighted the metabolic actions of NP in mouse and human studies which include for a large part the activation of catabolic processes [58]. NP have been shown to promote lipolysis and browning in WAT, activate brown fat thermogenesis, induce mitochondrial fat oxidative capacity and fat oxidation in skeletal muscle, inhibit food intake and reduce gastric emptying as summarized in Fig. 1 and Table 2.

3.1. Lipolysis

In light of a significant expression of NPR in WAT [59], our laboratory demonstrated a potent lipolytic effect of NP on human isolated adipocytes (reviewed in detail in Refs. [2,3]). The signaling pathway has been characterized and involves activation of the cGK-Iα which phosphorylates hormone sensitive lipase (HSL) and perilipin-1 to initiate the process of lipolysis [60]. This effect appears independent of cross-activation of the cAMP/PKA pathway and refractory to the anti-lipolytic effect of insulin *in vitro* [61] and *in vivo* [62]. We could also show that ANP contribute to the physiological control of lipid mobilization in humans to supply fatty acids to skeletal and cardiac muscle during exercise [25]. NP-dependent lipolytic activation in AT is attenuated in a number of pathophysiological conditions including overweight/obesity [63], polykystic ovary syndrome [64], and hypothyroidism [65]. In contrast, NP-mediated lipolysis increases during hyperthyroidism [65], in HF patients [66], and in cancer cachexia [67]. Interestingly, NP-mediated lipolysis seems to be a primate fat cell specificity

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Table 1
Human clinical studies linking circulating NP levels and metabolic diseases.

Study name	Sample	Main findings	References
The Framingham Heart Study	3389	Inverse correlation between plasma BNP/NT-proANP and BMI and T2D	[6]
The Olivetti Heart Study	787	Male subjects carrying the A(-55)A *Nprc* genotype have a significantly lower prevalence of overweight, obesity, and abdominal adiposity	[33]
The Dallas Heart Study	2971	Inverse relationship between plasma BNP and NT-proBNP and BMI	[100]
The FINRISK97 Study	7827	ANP, BNP and NT-proBNP belong to the 31 novel predictors of incident T2D	[101]
Meta-analysis of 11 case–control studies		Genetic variant rs198389 within the BNP locus is associated with a lower risk of developing T2D	[102]
Prevalence of left ventricular dysfunction study	1608	rs5068, a genetic variant of the ANP gene, is associated with cardiometabolic protection	[56]
Malmö Diet and Cancer study	1828	Low plasma level of ANP predicts the development of T2D	[10]
The Atherosclerosis Risk on Communities study	7822	High NT-proBNP levels are associated with reduced T2D risk	[11]
The Dallas Heart Study	2619	High NP levels are associated with a favorable adipose tissue distribution	[103]
Malmö Diet and Cancer study	27,307	Carriers of at least one copy of the G allele of rs5068 have reduced incident T2D risk over 14 years	[57]
The Diabetes Prevention Program	2411	Circulating NT-proBNP level correlates with insulin sensitivity before and during preventive interventions for T2D	[9]
Meta-analysis of 5 case–control studies		NT-proBNP is a predictor of cardiovascular diseases in T2D people	[104]
Outpatients visiting the National Center for Global Health and Medicine Kohnodai Hospital	60	Plasma BNP level is positively associated with physical activity levels	[26]

BMI: body mass index; T2D: type 2 diabetes.

because of the low NPRA-to-NPRC ratio in rodent adipocytes [68]. Adipocytes from NPRC knockout mice exhibit a normal lipolytic response to ANP [4].

Table 2
Metabolic phenotype of mouse models of NP gain- and/or loss-of-function.

Model	Phenotype	Biological effects	References
BNP-Tg	Prevention of diabetic nephropathy	↘ urinary albumin excretion ↘ glomerular hypertrophy	[105]
BNP-Tg	Resistance to DIO	↘ body fat mass ↘ TAG in liver/skeletal muscle ↘ fasting insulin and glucose ↗ fat oxidation	[35]
NPRA+/–	Susceptibility to DIO	↗ body fat mass ↘ glucose tolerance	[35]
NPRA–/–	Increased gastric emptying and absorption	↗ intra gastric pressure ↗ gastric contractility ↗ gastrointestinal permeability	[83]
NPRA–/–	Altered pancreatic β-cell function	↘ GSIS ↘ islet size ↘ β-cell mass ↘ insulin content ↗ fasting blood glucose	[81]
NPRC–/–	Increased thermogenesis	↘ fat mass ↗ thermogenic gene expression in brown and white fat	[4]
cGKI-Tg	Improved metabolic profile and resistance to DIO	↘ body weight gain ↘ TAG in liver/skeletal muscle ↗ fasting insulin and glucose ↗ oxygen consumption ↘ respiratory quotient ↗ muscle mitochondrial density	[35]
cGKI–/–	Liver inflammation and insulin resistance	↗ fasting hyperglycemia ↗ hepatic IL-6 signaling ↘ hepatic Akt phosphorylation ↘ serum adiponectin	[106]
NEP–/–	Protection against fat-induced pancreatic β-cell dysfunction	↗ GSIS ↗ calcium influx	[41]
GUCY2C –/–	Obesity and hyperphagia	↗ body weight gain ↗ fasting leptin and insulin ↘ daily food intake ↘ satiety	[91]

DIO: diet-induced obesity; GSIS: glucose-stimulated insulin secretion; TAG: triacylglycerol.

3.2. Thermogenesis

Lipolysis is also an important physiological process to fuel BAT thermogenesis. Recently, Bordicchia et al. demonstrated that acute cold exposure (6 h at 4 °C) robustly induces cardiac BNP secretion in mice [4]. This is concomitant with an induction of classical thermogenic genes such as the uncoupling protein 1 (UCP1) in inguinal WAT. Cold exposure in mice also facilitates NP signaling by increasing the ratio of NPRA-to-NPRC in white fat. In addition, NPRC knockout mice display reduced white fat pad weight and increased browning [4].

The underlying mechanism likely involves the activation of the p38 MAPK-ATF2 and peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC1α) pathway through cGK-I in human adipocytes [4]. cGK-I seems important for brown fat cell differentiation and thermogenesis by inducing mitochondrial biogenesis and UCP1 [69,70]. The relevance of this finding was demonstrated in human primary and hMADS adipocytes [4,71]. Activation of NP signaling in adipocyte increases oxygen consumption rate and activate mitochondrial oxidative gene expression. This process could involve AMPK [71]. Another study confirmed a significant increase of UCP1 expression reflecting a browning of white fat pads of db/+ and db/db mice chronically treated with BNP [72]. However both elevated plasma NP levels and cold exposure are known to activate the sympathetic nervous system. It is therefore unclear if NP directly control brown fat thermogenesis independently or synergistically with catecholamines. Further studies are needed to demonstrate the specific contribution of NP in the control of thermogenesis and white adipose tissue browning *in vivo* in mice.

3.3. Fat oxidation/energy expenditure

Miyashita et al. reported a few years ago that BNP-transgenic mice (overexpressing BNP plasma levels up to 100 times) were partly protected against high fat diet-induced weight gain. This was associated with an elevated rate of oxygen consumption and fat oxidation [35], possibly due to increased mitochondrial respiration in white/brown adipocytes and skeletal muscle cells. A similar phenotype was observed in cGK-I-transgenic mice (overexpressing cGK-I ubiquitously), thus confirming the link between NP signaling in metabolic organs and energy expenditure. Of interest, cGK-I-transgenic mice exhibited giant mitochondria with dense cristae in their skeletal muscles. Later, Engeli et al. demonstrated that chronic treatment of human primary myotubes with NP up-regulates PGC1α

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gene and protein expression, as well as mitochondrial oxidative genes and proteins, oxygen consumption, and fat oxidation [5]. Of note, NPRA expression positively correlates with PGC1α expression in human skeletal muscle and both genes are up-regulated in response to endurance exercise. This suggests that NP signaling may control mitochondrial fat oxidative capacity in skeletal muscle and could mediate some of the effects of exercise on skeletal muscle. Further studies should assess the role of NP in the physiological adaptations of skeletal muscle to acute and chronic exercise.

3.4. Insulin sensitivity

Consistent with an increased rate of oxygen consumption and resistance to diet-induced obesity, both BNP- and cGK-I-transgenic mice are also partly protected against diet-induced insulin resistance and glucose intolerance [35]. This was confirmed in another study showing that 12-weeks of BNP infusion in db/db mice improves insulin and glucose tolerance [72]. Although the underlying mechanisms were not investigated, increased NP levels and/or signaling were associated with reduced lipid accumulation in liver and skeletal muscle [35]. Thus additional studies are needed to investigate the mechanisms by which NP treatment improves insulin sensitivity and whether this is a direct effect on either skeletal muscle, liver and adipose tissue.

In addition, several studies reported an inverse relationship between insulin sensitivity and plasma NP levels in humans [8,9]. Little or no data are currently available on the link between insulin sensitivity and NP signaling in metabolic organs such as AT, skeletal muscle and liver. One study reported that ANP exhibit anti-inflammatory effects by inhibiting pro-inflammatory cytokines expression and secretion from human AT explants [73]. Specifically, ANP was shown to activate NPRA on adipose tissue macrophages and inhibit the secretion of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α. Considering that AT and systemic inflammation are associated with insulin resistance [74], this could be one mechanism by which ANP preserves insulin sensitivity in humans. Two studies also suggested that ANP enhances the secretion of the pro-insulin sensitizing adipokine adiponectin from adipocytes both *in vitro* and *in vivo* [75,76]. In summary, additional studies are required to assess the mechanistic link between NP signaling and insulin sensitivity in humans.

3.5. Insulin secretion

In 1986, Uehlinger and colleagues noted that a supra physiological infusion of ANP raises plasma insulin levels in human volunteers [77]. No effect was observed at a lower physiological dose [78]. Birkenfeld et al. also reported that ANP infusion at a physiological dose significantly increases plasma insulin levels during a meal test in lean healthy volunteers [79]. Studies in rodents identified the presence of NPRA in α and β pancreatic cells. Thus in mouse isolated islets, ANP apparently increases glucose-stimulated insulin secretion [80,81]. NP signaling through NPRA may be important to maintain β-cell mass since islets from NPRA knockout mice display reduced islet size, β-cell number and insulin content [81]. Together, it is unclear if NP enhance insulin secretion in a physiological setting and how they could impact on the endocrine pancreas. This area of research requires further investigations.

3.6. Nutrient absorption

Addisu et al. reported that high circulating levels of BNP in mice undergoing myocardial infarction of the left ventricle exhibit a reduced gastric emptying and intestinal absorption [82]. These effects are abolished in NPRA knockout mice. Moreover, intravenous BNP injection dose-dependently inhibits gastric emptying in mice [83]. ANP infusion directly into antral mucosal segments of rat stomach also induces somatostatin secretion in a NPRA-dependent manner [84]. Somatostatin inhibits the synthesis and secretion of peptide hormones in a wide variety of neuroendocrine cells and is a negative regulator of ghrelin secretion [85]. Plasma ghrelin levels were significantly lower in patients with congestive HF and correlated negatively with NT-proBNP levels [86]. More recently, Vila et al. reported that intravenous BNP infusion reduces total and acylated ghrelin plasma concentrations in healthy volunteers [87]. In summary, through their action on the gastro-intestinal system, NP may also impact on whole-body energy metabolism by modulating metabolic and satiety hormone levels.

3.7. Food intake

CNP is the most abundant member of the NP family present in the brain [88]. CNP is widely expressed in discrete hypothalamic areas such as the arcuate nucleus of the hypothalamus that play a key role in the central control of energy metabolism. NPRB, which binds CNP, is also the main NPR expressed in rat hypothalamus [89]. Interestingly, intra-cerebro-ventricular administration of CNP significantly suppresses food intake. This effect is abrogated by co-administration of CNP and the melanocortin-3 receptor (MC3R)/melanocortin-4 receptor (MC4R) antagonist SHU9119 [90]. This suggests that CNP may inhibit food intake through activation of anorexigenic POMC neurons in the arcuate nucleus of the hypothalamus. In addition, CNP antagonizes orexigenic NPY neurons as well as the effect of the orexigenic hormone ghrelin [90]. Recently, Valentino and coworkers elegantly demonstrated that uroguanylin, a distant member of NP family, binding to a transmembrane guanylyl cyclase receptor (GC-C), inhibits food intake in a cGMP-dependent manner through modulation of POMC neurons [91]. Vila et al. also reported that intravenous BNP infusion in healthy volunteers increases satiety scores and inhibit food intake [87]. Future studies should assess whether NP can directly impact on hypothalamic neurons to modulate food intake.

4. Restoring the natriuretic handicap

As discussed earlier, the natriuretic handicap is defined as a combination of reduced cardiac NP secretion and/or increased systemic and tissue clearance in obesity. The reduced plasma NP level observed in obesity seems to be reversible. Previous studies demonstrated that low calorie diet [92] and endurance exercise training [63] can improve ANP-mediated lipolysis in overweight and obese individuals. Although the molecular mechanisms have not yet been investigated in detail, it is possible that the natriuretic handicap at the tissue level includes both a reduced NPRA expression/signaling and an increased NPRC expression. In line with this, 8-week of aerobic exercise training raises NPRA mRNA levels in skeletal muscle of obese individuals [5]. However, no change in resting concentrations of ANP and BNP were noticed in this study after exercise training. Thus lifestyle interventions combining regular sessions of physical exercise and calorie restriction to favor weight loss could prove useful to increase circulating NP levels and normalize NPRC expression in white adipose tissue [93]. It was shown that the early phase of weight loss induced by calorie restriction is associated with natriuresis, reduction in blood pressure and a doubling of plasma ANP levels in overweight normotensive subjects [94]. Intense lifestyle intervention including dietary counseling, exercise, stress management and social support increases circulating BNP concentrations in subjects with coronary heart disease or at high risk [95]. Importantly, individuals who lost

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most weight in response to the 3-months lifestyle intervention had the greatest increase in plasma BNP levels. In addition, obese subjects undergoing laparoscopic gastric bypass surgery display an increase in plasma BNP and NT-proBNP levels that correlate significantly with weight loss [96–98]. Changes in NP levels were not secondary to underlying cardiac changes but were attributable to the weight loss *per se* [99]. In summary, although further studies are needed to characterize the molecular defects of NP signaling in obesity, lifestyle interventions combining exercise and calorie restriction at least partly restore the natriuretic handicap in parallel of improving the metabolic status.

5. Conclusion and future directions

Over the last decade, NP have emerged as key metabolic hormones. NP target a variety of organs to regulate energy metabolism (Fig. 1). It is now well accepted that obesity and T2D are accompanied by a "natriuretic handicap" which includes a combination of lower cardiac qualitative and quantitative NP secretion and an accelerated clearance rate by peripheral organs such as AT. This concept is so far well supported in mouse studies and needs to be confirmed in humans. It could be therefore of therapeutic interest to restore circulating NP levels and tissue response in metabolic disorders. Importantly, the identification of the presence of NPRA in multiple metabolic organs such as skeletal muscle, liver, pancreas and BAT, will lead to discover novel biological roles of this family of cardiac hormones. The robust and reproducible link observed in cohort studies between plasma NP levels and incidence of T2D should foster research efforts to unravel the target organs and underlying molecular mechanisms.

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