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Metabolic actions of natriuretic peptides and therapeutic potential in the metabolic syndrome

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ABSTRACT

Natriuretic peptides (NPs) are a group of peptide-hormones mainly secreted from the heart, signaling via c-GMP coupled receptors. NP are well known for their renal and cardiovascular actions, reducing arterial blood pressure as well as sodium reabsorption. Novel physiological functions have been discovered in recent years, including activation of lipolysis, lipid oxidation, and mitochondrial respiration. Together, these responses promote white adipose tissue browning, increase muscular oxidative capacity, particularly during physical exercise, and protect against diet-induced obesity and insulin resistance. Exaggerated NP release is a common finding in congestive heart failure. In contrast, NP deficiency is observed in obesity and in type-2 diabetes, pointing to an involvement of NP in the pathophysiology of metabolic disease. Based upon these findings, the NP system holds the potential to be amenable to therapeutical intervention against pandemic diseases such as obesity, insulin resistance, and arterial hypertension. Various therapeutic approaches are currently under development. This paper reviews the current knowledge on the metabolic effects of the NP system and discusses potential therapeutic applications.

Contents

Abbreviations: ACE, angiotensin converting enzyme; AMPK, adenosine monophosphate-activated protein kinase; ANP, atrial natriuretic peptide; ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; BAT, brown adipose tissue; BMI, body mass index; BNP, brain-type natriuretic peptide; cAMP, cyclic adenosine monophosphate; cGK-I, protein kinase G; cGMP, cyclic guanosine monophosphate; CHF, chronic heart failure; CNP, C-type natriuretic peptide; DAG, diacylglycerol; DNP, dendroaspis natriuretic peptide; FFA, free fatty acid; GC, guanylyl cyclase; GFR, glomerular filtration rate; GLP-1R, glucagon-like peptide-1 receptor; HDL, high density lipoprotein; HFD, high fat diet; HMW, high molecular weight; HSL, hormone sensitive lipase; IgG, immunoglobulin G; LDL, low density lipoprotein; LVH, left ventricular hypertrophy; MR-pro-ANP, mid-regional pro-atrial natriuretic peptide; NEP, neutral endopeptidase; NP, natriuretic peptides; NPRA, natriuretic peptide receptor A; NPRB, natriuretic peptide receptor B; NPRC, natriuretic peptide receptor C; NPY, neuropeptide Y; NRF, nuclear respiratory factor; NT-proANP, N-terminal prohormone of atrial natriuretic peptide; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; p38 MAPK, p38 mitogen activated protein kinase; PDE3B, phosphodiesterase 3B; PDE5, phosphodiesterase 5; PEG, polyethylene glycol; PGC-1α, prolifator-activated receptor γ coactivator 1α; PKA, protein kinase A; PKC, protein kinase C; PPAR-δ, peroxisome proliferator activated receptor δ; RAAS, renin–angiotensin–aldosterone-system; SAT, subcutaneous adipose tissue; T2DM, type 2 diabetes mellitus; UCP 1, uncoupling protein 1; UCP 3, uncoupling protein 3; VAT, visceral adipose tissue; WAT, white adipose tissue.

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1. Introduction

Natriuretic peptides (NP) are primarily known for their cardiovascular and renal actions. Moreover, NP or their fragments are widely applied as cardiovascular biomarkers in epidemiological studies and in the clinical routine setting. In particular, NP are important in the diagnostic workup of heart failure patients (Maisel et al., 2002). However, during the last decade, NPs have been shown to exert a variety of metabolic effects. The purpose of the present review is to give an overview of the current knowledge of the metabolic properties of NP and to summarize therapeutic options that arise from these findings in the treatment of the metabolic syndrome and its components.

2. The natriuretic peptide system

2.1. Components and receptor tissue distribution

The endocrine properties of the heart were first discovered by deBold in 1981 when intravenous infusion of a crude atrial myocardial extract into rats led to a potent natriuretic and diuretic effect (deBold et al., 1981). Twenty-five years earlier, granules resembling endocrine glands had been discovered in atrial myocardium using electron microscopy (Kisch, 1956). Three years after the ground-breaking discovery by deBold, the structure of the underlying peptide was identified and designated 'atrial natriuretic peptide' (ANP) (Kangawaet al., 1984a, 1984b, 1984c). Within the following years, a number of structurally and functionally related peptides have been identified to comprise the NP-hormone family.

To date three members of the NP family, atrial natriuretic peptide (ANP), brain-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), are considered to play a role in metabolic regulation. All three natriuretic peptides are secreted as pro-hormones and cleaved by proteases to reach their final, biologically active form. The three peptides have a 17-amino acid ring structure in common, formed by a disulfide bond between two cysteinyl residues. In humans, the amino acid sequence of the ring structure is highly preserved within the three peptides, differing by a few amino acid molecules, only. Both, ANP and BNP feature peptide specific amino- and carboxy-terminal extensions, while CNP lacks the carboxy-terminal appendage (Nishikimi et al., 2011). ANP is predominantly released from atrial myocardium where it is produced as a preprohormone and stored as a proANP in intracellular granules (Nakao et al., 1992). The biologically active αANP is a 28-amino acid peptide cleaved from proANP by the serine-protease corin during secretion (Yan et al., 2000). Brain-type natriuretic peptide was first discovered in porcine brain (Sudoh et al., 1988). Today, BNP is known to be primarily secreted by ventricular myocardium (Nannipieri et al., 2002). Similar to ANP, BNP is produced as preproBNP which is then cleaved to proBNP. Eventually conversion of proBNP to active, 32-amino acid BNP is mediated by the endoprotease furin at the trans-Golgi network (Nakayama, 1997). Lacking the carboxy-terminal extension, CNP is the shortest member of the NP family, comprising 22-amino acid residues, only (Nishikimi et al., 2011). It was initially identified in porcine brain (Sudoh et al., 1990). CNP is predominantly present in vascular endothelial cells and in the central nervous system (Komatsu et al., 1991; Heublein et al., 1992; Stingo et al., 1992; Suga et al., 1992). Further members of the NP family are urodilatin, which has been isolated from urine, and Dendroaspis Natriuretic Peptide (DNP) from the venom of green mamba snakes (Dendroaspis angusticeps) (Mitsuishi et al., 2008; You & Laychock, 2011). Urodilatin and DNP have not been well studied upon metabolic effects in humans and, thus, shall not be further discussed in this review.

Circulating ANP and BNP concentrations may differ between healthy men and women (Vasan et al., 2002; Clerico et al., 2005; Lam et al., 2011). NPs increase progressively throughout adolescence in girls, and reach about 2-fold higher levels in normal cycling women compared to men at the same age (Maffei et al., 2001; Clerico et al., 2002), in some but not all studies. The ANP-precursor gene, NPPR, interacts with estradiol receptor-α (ER-α) (Mahmoodzadeh et al., 2012). Moreover, estrogen administration in postmenopausal women increases circulating ANP levels (Maffei et al., 2001). Besides regulating NP transcription and secretion, estrogens also seem to affect NP-receptor expression. Estradiol augments Natriuretic peptide receptor A (NPRA) expression levels, while stabilizing or reducing Natriuretic peptide receptor C (NPRC) transcription levels, in a tissue and setting dependent manner in mice (Belo et al., 2008). Possibly, sex dependent NP regulation contributes to the well-known differences in cardiovascular risk, sympathovagal balance and redistribution of body fat between women and men, as explained in detail below.

2.2. Natriuretic peptide signaling cascade

NPs exert their effects via NP receptors in a classical endocrine manner. Three subtypes of NP receptors have been described. Natriuretic peptide receptors A and B (NPRA and NPRB) are guanylyl cyclase (GC) coupled transmembrane receptors (Waldman et al., 1984; Song et al., 1988). Ligand binding to NPRA and -B activates the cytosolic GC receptor domain increasing intracellular levels of the second messenger cGMP. NPRC, the third NP receptor subtype, does not have GC activity, facilitating NP internalization and degradation, instead (Maack et al., 1987). Therefore, NPRC is sometimes referred to as clearance receptor. Additionally, NP are cleared by the neural endopeptidase neprilysin (NEP) (alternative names: atriopeptidase, common acute lymphocytic leukemia antigen (CALLA), enkephalinase, neutral endopeptidase 24.11) (Kenny et al., 1993).

The diverse effects of the NP system are determined by NP receptor distribution and receptor-ligand-affinity and are depicted in part in Fig. 1. NPRA is regarded as the main effector receptor for ANP and BNP (Suga et al., 1992). NPRA is abundantly expressed in vascular smooth muscle and endothelial cells, adipose tissue as well as in kidney, adrenal gland, liver and brain and to a lesser extent in the heart (Sarzani et al., 1996; Bryan et al., 2006). NPRB is structurally similar to NPRA but is rather activated by CNP in a paracrine fashion (Koller et al., 1991; Suga, Nakao, Hosoda, et al., 1992). NPRB is expressed by chondrocytes, where it appears to play a crucial role in enchondral ossification during long bone growth (Yasoda et al., 1998). Disruption of the CNP/NPRB-signaling in mice leads to dwarfism (Chusho et al., 2001; Tsuji & Kunieda, 2005), while CNP overexpression is associated with bone overgrowth (Kake et al., 2009). Apart from bone, NPRB is highly expressed in brain, lung, heart, ovary tissue fibroblasts and vascular smooth muscle cells (Schulz et al., 1989; Nagase et al., 1997). The NP clearance receptor C is mainly present in adipose tissue and kidney (Nagase et al., 1997). NPRC is involved in degradation of all three types of natriuretic peptides with highest affinity to ANP and lowest affinity to BNP (Suga et al., 1992).

3. Cardiovascular effects of natriuretic peptides

The beneficial effects of NPs on systemic blood pressure and cardiac remodeling have been investigated thoroughly. The present review focuses on the metabolic properties of the NP system and the resulting therapeutic implications. However cardiovascular disease and metabolic disorders are tightly linked. Therefore the various mechanisms involved in NP mediated blood pressure regulation will be outlined briefly.

As ligands for the same receptor, ANP and BNP appear to maintain similar regulatory actions on blood pressure and cardiac remodeling. However, ANP and BNP markedly differ in plasma half-life times, with BNP having an approximately sevenfold longer half-life period (21 min) than ANP (3 min) (Astrup et al., 1985). The difference in half-life might be explained by faster clearance of ANP due to a greater NPRC affinity compared to BNP.

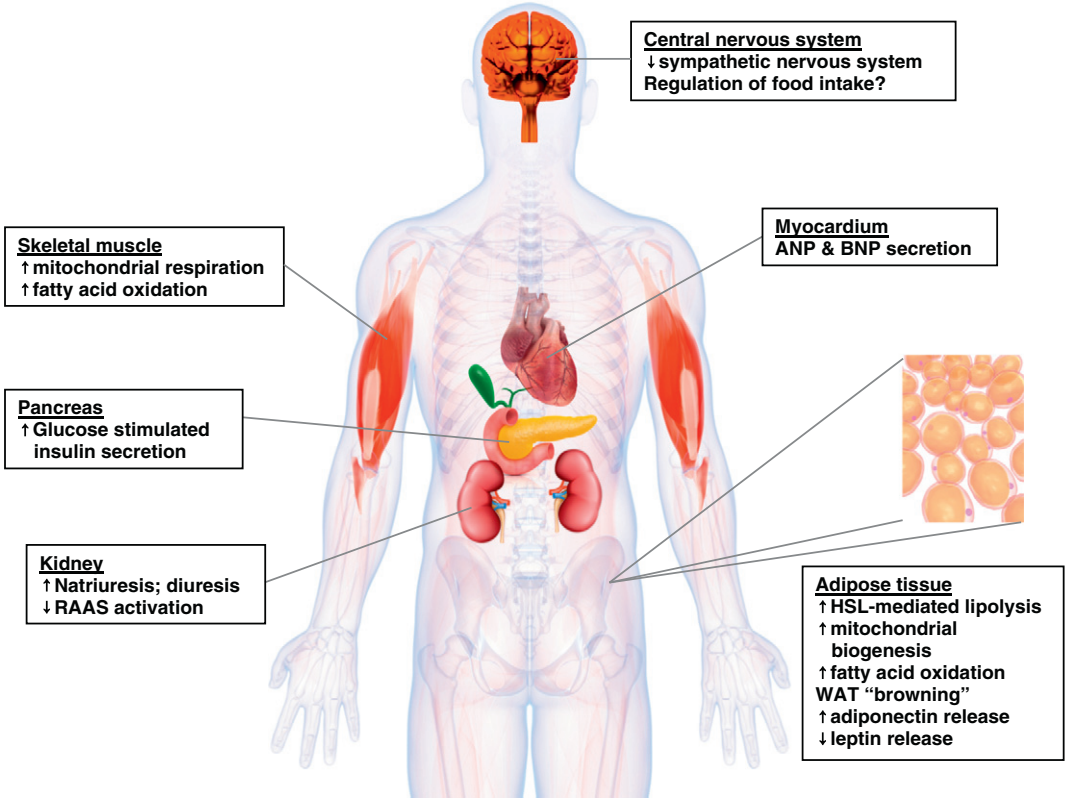

Fig. 1. Target organs of the natriuretic peptide system. Released by the heart in response to cardiac wall stress, natriuretic peptides act on vascular system, kidneys and brain. In order to reduce blood pressure and the resulting cardiac burden, NPs reduce vascular tone, enhance renal sodium and water excretion, inhibit the renin–angiotensin–aldosterone system (RAAS) and attenuate central nervous sympathetic nervous system activity. Moreover, natriuretic peptides exert metabolic effects in a numerous organs. In human adipose tissue, NPs enhance lipolysis as well as the secretion of the insulin sensitizing adipokine adiponectin, while leptin release is suppressed. At the same time, natriuretic peptides enhance mitochondrial biogenesis and oxidative capacity in skeletal muscle and adipose tissue. In white adipose tissue (WAT) mitochondrial biogenesis leads to browning of adipocytes, enhancing energy expenditure and heat production. Natriuretic peptides might also improve pancreatic insulin secretion. All these mechanisms might play together to control whole body energy homeostasis. ANP atrial natriuretic peptide; BNP brain natriuretic peptide; HSL hormone sensitive lipase.

Both, ANP and BNP reduce systemic vascular tone in a dose dependent manner (Protter et al., 1996; van der Zander et al., 1999). Mice with endothelium restricted NPRA deletion feature arterial hypertension with a paradoxically normal vasodilatory response to ANP (Sabrane et al., 2005). Endothelial NPRA appears to affect endothelial permeability, thus, regulating fluid shifts between the interstitial and intravascular compartment (Sabrane et al., 2005). Cardiomyocyte restricted NPRA disruption in mice is associated with five times higher ANP concentrations compared to wild type and comes along with markedly reduced blood pressure levels (Holtwick et al., 2003). Heart specific NPRA disruption was also associated with pressure independent cardiac hypertrophy, confirming anti-cardiohypertrophic properties of NP (Tamura et al., 2000; Kishimoto et al., 2001; Holtwick et al., 2003). Moreover, NPs acutely reduce plasma volume in part by enhancing natriuresis (Yoshimura et al., 1991). ANP augments glomerular filtration rate (GFR) through escalation of glomerular capillary pressure and expansion of mesangial cell filtration surface (Fried et al., 1986; Marin-Grez et al., 1986). Additionally, NPs inhibit water and sodium re-uptake in the proximal tubule and the collecting duct (Sonnenberg et al., 1986; Harris et al., 1987).

In addition to the direct cardiovascular and renal effects, NPs inhibit the renin–angiotensin–aldosterone-system (RAAS) by suppressing renal renin release (Burnett et al., 1984; Johnson et al., 1988; Shi et al., 2001). Besides peripheral regulatory effects on blood pressure, NPs modulate sympathetic activity in the central nervous system (Floras, 1990; Schroeder et al., 2006). CNP does not seem to have a significant effect on renal sodium and water excretion (Pham et al., 1997). However, CNP is considered to cause vascular smooth muscle relaxation and inhibition of smooth muscle proliferation in a paracrine manner (Furuya et al., 1990; Furuya et al., 1991). Yet, CNP−/− mice do not develop severe arterial hypertension, indicating that CNP might not play an important role in blood pressure and fluid homeostasis (reviewed by Schulz) (Schulz, 2005).

4. Metabolic effects of natriuretic peptides

4.1. Natriuretic peptide activated lipolysis

The regulation of lipolysis in adipose tissue has been thoroughly investigated (Lafontan & Langin, 2009; Ahmadian et al., 2010; Zechner et al., 2012). For many years, catecholamines were considered to be the major physiological lipolytic agent. Catecholamines induce lipolysis via stimulation of adipocyte adrenergic β-receptors and subsequent cAMP dependent activation of hormone sensitive lipase (HSL) (Stralfors & Belfrage, 1983; Stralfors et al., 1984; Egan et al., 1992). The exact mechanism of adipose triglyceride lipase (ATGL) activation in the process, hydrolyzing the first fatty acid from triacylglycerols, is still a matter of research (Zechner et al., 2012). Insulin is the major endogenous inhibitor of catecholamine dependent lipolysis (Coppack et al., 1989; Jensen et al., 1989). Insulin abolishes adipose tissue lipolysis via phosphodiesterase 3B (PDE3B) activation which subsequently leads to cAMP degradation and deactivation of PKA (Choi et al., 2006).

A decade ago, NP entered the 'lipolytic arena'. Potent lipolytic properties of natriuretic peptides were first described by Sengenès et al. (2000). The authors observed that all three subtypes of the NP family promote lipolysis in human adipose tissue, with ANP being the most potent activator of lipolysis, followed by BNP and CNP in descending order (pEC50: ANP 9.82 ± 0.20; BNP 8.33 ± 0.08; CNP 7.75 ± 0.58 [−log EC50]).

Lipolytic NP actions appear to be limited to primates owing to higher NPRC expression in other mammalian adipocytes (Sengenès et al., 2002). Indeed; NPRC deletion fully restored the lipolytic properties of natriuretic peptides in mice (Bordicchia et al., 2012).

Unlike catecholamines, NPs resort to a cGMP dependent, protein kinase G activating, pathway. NP driven activation of protein kinase G (GK-I) promotes perilipin A and hormone sensitive lipase (HSL) mediated triglyceride degradation (Sengenès et al., 2000, 2003; Birkenfeld et al., 2005). Relying on different pathways, the lipolytic actions of NP's and catecholamines in humans seem to be completely independent (Galitzky et al., 2001; Birkenfeld et al., 2006). Simultaneous stimulation with ANP and β-adrenergic agonists such as isoproterenol results in additive potentiation of the lipolytic effects in human adipocytes (Moro et al., 2004).

Remarkably, insulin does not seem to have a direct antilipolytic effect on the cGMP/GK-I dependent lipolytic pathway (Moro et al., 2004; Moro et al., 2005).

However, insulin might attenuate NP mediated lipolysis indirectly by reducing circulating NP levels. Furthermore, insulin may reduce NPRA expression while reciprocally enhancing NPRC expression in white adipose tissue in rodents and humans (Nakatsuji et al., 2010; Pivovarova et al., 2012). In fact, short-term insulin infusions reduced circulating NT-pro-BNP and MR-pro-ANP levels in humans (Halbirk et al., 2010; Pivovarova et al., 2012) and interventions increasing insulin sensitivity increase MR-pro-ANP levels (Rudovich et al., 2012).

Besides direct activation of lipolysis, other relevant effects on adipose tissue have been described. Sarzani et al. hypothesized that ANP may attenuate human adipocyte growth (Sarzani et al., 2007). However, this issue needs further study to fully delineate the effect of NPs in adipogenesis. Moreover, Moro and colleagues showed that ANP inhibits the release of pro-inflammatory cytokines and chemokines from human adipocytes and adipose tissue macrophages (Moro et al., 2007). The mechanism could be beneficial because chronic, low grade inflammation contributes to obesity-associated insulin resistance and cardiovascular disease.

4.2. Natriuretic peptides enhance lipid oxidation and mitochondrial respiration

NP induced lipolysis acutely increases free fatty acid (FFA) availability in human subjects (Galitzky et al., 2001; Birkenfeld et al., 2005, 2006, 2011a). Apparently, these fatty acids serve as substrates for oxidative tissues such as skeletal muscle, liver, and 'beige' and brown adipose tissue. Moreover, studies in humans and mice indicate that NPs enhance lipid oxidation in adipose tissue, skeletal muscle and liver, allowing these tissues to fuel fatty acids into the β-oxidation pathway at an increased rate.

We observed that short term intravenous administration of ANP acutely increases lipid oxidation (Birkenfeld et al., 2005, 2012) and postprandial energy expenditure in healthy men (Birkenfeld et al., 2008). In the latter study, circulating beta-hydroxybutyrate increased markedly, indicating that hepatic lipid oxidation at least in part contributed to the acute response. Molecular mechanisms might include distinct pathways. First, FFAs from acute β-adrenergic receptor mediated lipolysis seem to increase mitochondrial respiration and lipid oxidation by an effect on uncoupling protein 3 (UCP3) activity in skeletal muscle (Hoeks et al., 2003). The mechanism might also be applicable to the NP system. Second, apart from acute lipid oxidation enhancement (Birkenfeld et al., 2008), ANP and BNP induce skeletal muscle mitochondrial biogenesis, respiration and lipid oxidation in human cells and in rodents, in vitro and in vivo (Miyashita et al., 2009). Chronic overexpression of BNP and GK-I each led to increased muscle mitochondrial content, oxidative capacity and lipid oxidation in mice. Enhanced oxidative metabolism was associated with protection from high fat diet (HFD) induced obesity and insulin resistance. Heterozygous NPRA knockout was associated with increased susceptibility to weight gain and insulin resistance in mice (Miyashita et al., 2009). The mechanism driving improvements in mitochondrial biogenesis and lipid oxidation in skeletal muscle included the induction of peroxisome proliferator–activated receptor γ coactivator (PGC)-1α and peroxisome proliferator–activated receptor (PPAR)-δ genes, two master regulators of mitochondrial biogenesis in skeletal muscle (Miyashita et al., 2009).

In human myotubes, we showed that ANP and BNP, as well as cGMP analogs, induced PGC-1α, mitochondrial respiration and lipid oxidation (Engeli, et al., 2012). Furthermore, NPRA expression was associated with PGC-1α expression in skeletal muscle of healthy physically trained human subjects. Supporting evidence comes from cell culture studies showing that cGMP restores glucose and insulin induced mitochondrial dysfunction in cultured C2C12 myotubes (Mitsuishi et al., 2008). In the same vein, nitric oxide signals via cGMP to mediate the induction of PGC-1α and mitochondrial biogenesis in various murine tissues (Nisoli et al., 2003). Activation of PGC-1α enhances activity of PPARs, nuclear receptors with transcriptional activity on genes involved in lipid oxidation and mitochondrial function (Puigserver et al., 1999; Schupp & Lazar, 2010). Moreover, mitochondrial biogenesis requires expression of nuclear encoded mitochondrial genes that are under the control of several transcription factors including the nuclear respiratory factors (NRFs) (Kelly & Scarpulla, 2004). PGC-1α is a key regulator of NRF-1 and 2, which control a network that includes respiratory chain subunits and parts of mitochondrial DNA transcription machinery (Kelly & Scarpulla, 2004). Importantly, PGC-1α also induces mitochondrial UCP1 in adipose tissue and UCP3 in skeletal muscle through interaction with PPARγ (Puigserver et al., 1999). Intriguingly, ANP and BNP not only induced PGC-1α expression in human myotubes, but also an array of downstream target genes, such as NRF1, UCP-3 and complexes I and IV of the respiratory chain (Engeli, et al., 2012). Together, these data suggest, that NPs induced lipid oxidation and mitochondrial respiration in skeletal muscle is induced through a cGMP driven, GK-I mediated effect on PGC-1α, inducing transcription of downstream targets, such as NRF-1 and UCP3, probably via PPARα and/or PPARδ. The signaling cascade is depicted in Fig. 2.

In white and 'beige' (brite) adipose tissue, NPs mediate similar effects (see below). In these tissues, activation of p38 mitogen activated protein kinase (p38 MAPK) by GK-I might play a role (Bordicchia et al., 2012). Moreover, Souza et al. showed that ANP induces mitochondrial biogenesis and up-regulates expression of mitochondrial genes involved in fatty acid transport and oxidation in human adipocytes via NPRA by GK-I dependent activation of AMP-activated protein kinase (AMPK) (Souza et al., 2011), a master energy sensor acting as a nod in intracellular energy metabolism. AMPK induces PGC-1α via direct phosphorylation to increase transcriptional activity of PGC-1α (Jäger et al., 2007). AMPK is generally induced via an increased ratio of AMP to ATP, or calcium via distinct kinases. More studies are clearly needed to put the pieces together. Identification of the initial molecular mechanisms involved in NP enhanced mitochondrial respiration may lead to novel targets for the treatment of metabolic disease.

4.3. Natriuretic peptides and browning of white adipose tissue

Recently, the significance of mitochondrial metabolism in adipose tissue has been revisited by showing that brown adipose tissue mass and function is more relevant in humans than previously appreciated. Moreover, adipocytes in human white adipose tissues can switch from white to brown and vice versa ('brite' or 'beige' adipose tissue) (Cypess et al., 2009). Fat is mainly stored in white adipose tissue (WAT). Brown adipose tissue (BAT) is another fat reservoir, which in contrast to WAT is able to generate heat and maintain body temperature. Brown adipocytes are located in the BAT and smaller populations were identified within WAT. BAT evolved in mammals to dissipate large amounts of biochemical energy in form of heat for defending the cold (Smith & Roberts, 1964). Upon cold exposure, BAT is activated by central nervous mechanisms through the sympathetic nervous system.

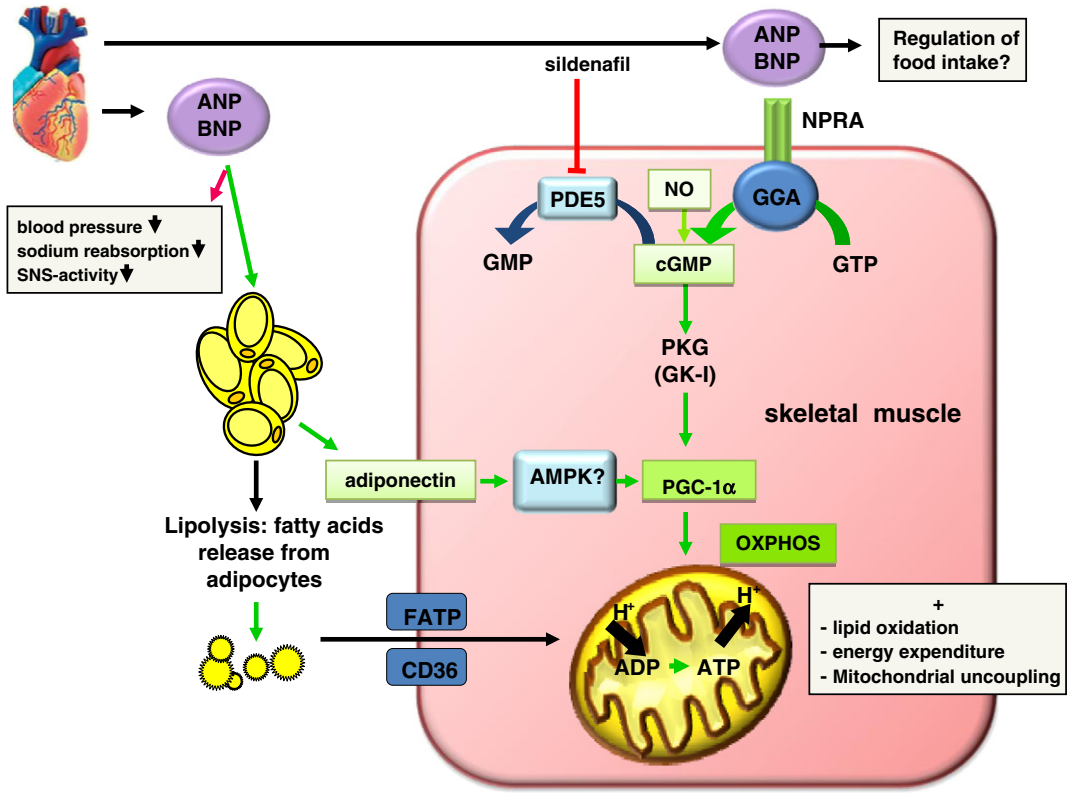

Fig. 2. Natriuretic peptide induced effects in skeletal muscle. ANP and BNP binding to the natriuretic peptide receptor A (NPRA) kicks of cGMP formation at the intracellular guanylyl cyclase receptor domain. Rising intracellular cGMP levels induce expression of PGC1α downstream genes. Moreover free fatty acids from adipocyte lipolysis serve as additional ligands for the transcriptional regulator of mitochondrial biogenesis PPARδ. Thus, natriuretic peptides increase muscle mitochondrial content and mitochondrial lipid oxidation. SNS sympathetic nervous system; ANP atrial natriuretic peptide; BNP brain type natriuretic peptide; NPRA natriuretic peptide receptor A; GTP guanosine triphosphate; cGMP cyclic guanosine monophosphate; GC-A guanylyl cyclase A; PGC1α Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; OXPHOS oxidative phosphorylation; ADP adenosine diphosphate; ATP adenosine triphosphate AMPK AMP-activated protein kinase; FATP fatty acid transport protein; CD36 cluster of differentiation 36 (=fatty acid translocase), green arrow indicates activation, induction, red arrow indicates decrease, inhibition.

The thermogenic response in brown adipocytes is mediated by uniquely enriched mitochondria expressing UCP1 in the inner membrane (Ricquier & Kader, 1976; Heaton et al., 1978; Lin & Klingenberg, 1980; Ricquier et al., 1983). UCP1 allows brown adipocytes to dissipate the electrochemical gradient that is normally used to drive ATP synthesis (Klingenberg, 1999). However, the thermogenic response cannot solely be explained by UCP1, since the expression of several genes involved in energy metabolism is increased in experimental animals to a cold environment (Stralfors & Belfrage, 1983; Egan et al., 1992). Bordicchia et al. recently demonstrated the importance of NPRA and NPRB in BAT (Bordicchia et al., 2012).

Adrenergic stimulation increases energy dissipation in BAT, probably reducing body weight in obese individuals (Astrup et al., 1985; Finer et al., 2000). However, adrenergic compounds have the potential to increase stroke and myocardial infarction risk, likely through influences on heart rate and blood pressure (Haller & Benowitz, 2000; Torp-Pedersen et al., 2007). Catecholamines raise intracellular cAMP, directly activating PKA (cAMP dependent protein kinase), which phosphorylates HSL and kinases of the p38 MAPK pathway (Cao et al., 2001, 2004). p38 MAPK inhibition attenuates adrenergically mediated UCP1 expression (Cao et al., 2004). Bordicchia et al. demonstrated that mice, lacking the negative regulator of NP activity NPRC−/−, have reduced WAT and lipid accumulation in BAT with enhanced expression of thermogenic genes in both tissues (Bordicchia et al., 2012). Treatment of a human derived adipocyte cell line with ANP results in GK-I dependent induction of thermogenic and mitochondrial genes, leading to an uncoupling of respiration (Bordicchia et al., 2012). NPs elicited the response by increasing p38 MAPK signaling and phosphorylation of ATF2, directly increasing UCP1 transcription in brown adipocytes (Bordicchia et al., 2012). BNP treatment in mice enhanced energy expenditure and increased thermogenic protein levels in BAT and WAT (Bordicchia et al., 2012). With cold exposure, circulating NP levels and BAT NPRA expression increases while NPRC expression decreases (Bordicchia et al., 2012). Similarly, forced GK-I expression in primary adipocytes induces a strong increase in UCP-1 and activates a brown-like thermogenic program. Treatment of mice with the phosphodiesterase 5 inhibitor sildenafil elicited a similar response (Pfeifer et al., 2013). Together, these studies show that similarly to skeletal muscle, the NP system induces a thermogenic program in adipose tissue. A schematic representation is given in Fig. 3. By these means, the NP axis seems to be involved in the physiological BAT adaptation to changes in environmental temperature (Carey & Kingwell, 2013; Schulz & Tseng, 2013).

4.4. Natriuretic peptide interactions with adipokines

Besides a direct activating effect on lipolysis and lipid oxidation, NPs also seem to have a regulatory sway on certain adipokines involved in energy metabolism. ANP acutely increases systemic levels of total and high molecular weight (HMW) adiponectin, an insulin sensitizing adipokine, in human subjects (Tanaka et al., 2008; Birkenfeld et al., 2012). These findings are in accordance with a number of observational studies showing positive associations between circulating NP and adiponectin levels, as for example in heart failure patients (Kistorp et al., 2005; Hara et al., 2011; Azizi Ghanbari et al., 2013). Leptin may be another NP regulated adipokine. ANP reduces leptin release from human adipocytes (Fain et al., 2003). These findings are supported in vivo by a recent clinical investigation. Melenovsky and coworkers observed a significant inverse relationship between systemic BNP levels and plasma concentrations of the anorexigenic adipokine leptin in heart failure patients (Melenovsky et al., 2013). To date, the mechanism

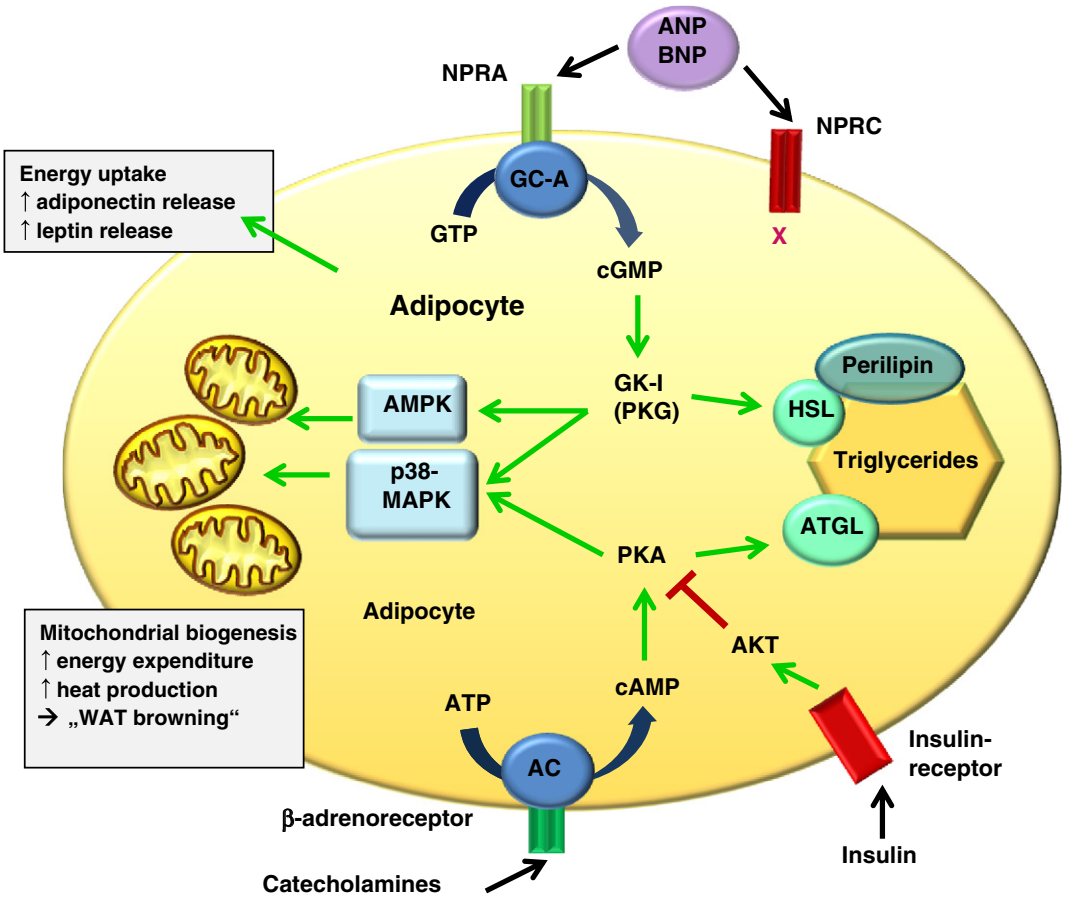

Fig. 3. NP related effects in human adipocytes. ANP and BNP induce a cGMP dependent pathway via stimulation of natriuretic peptide receptor A. Increased intracellular cGMP levels activate cGMP dependent protein kinase G which induces lipolysis through phosphorylation of hormone sensitive lipase. At the same time, enhances mitochondrial biogenesis via activation of AMPK and p38-MAPK, leading to browning of white adipose tissue. Unlike catecholamine induced lipolysis, the cGMP dependent lipolytic pathway is independent of the antilipolytic effects of insulin. ANP atrial natriuretic peptide; BNP brain type natriuretic peptide; NPRA natriuretic peptide receptor A; NPRC natriuretic peptide receptor C; GCA guanylyl cyclase A; GTP guanosine triphosphate; cGMP cyclic guanosine monophosphate; PKG protein kinase G; ATP adenosine triphosphate; AC adenylyl cyclase; cAMP cyclic adenosine monophosphate; PKA protein kinase A; HSL hormone sensitive lipase; ATGL adipocyte triglyceride lipase; AMPK AMP-activated protein kinase; p38-MAPK mitogen-activated protein kinase; AKT protein kinase B.

and significance of NP adipokine release is still incompletely understood. In conditions with decreased NP levels, such as in obesity, the mechanism might contribute to metabolic disease (Wang, 2012).

4.5. Natriuretic Peptides, insulin secretion and glucose homeostasis

A number of studies suggest that NP directly and indirectly affect glucose metabolism. We and others observed increased insulin levels during ANP infusion in human subjects (Uehlinger et al., 1986; Birkenfeld et al., 2005, 2008). The effect might be explained by a direct modulating effect on β-cell function or, less likely in the acute setting, on β-cell mass (Ropero et al., 2010). ANP directly enhanced glucose-stimulated insulin secretion in cultured islets. In addition, ANP induced β-cell growth in isolated rat pancreatic islets (You & Laychock, 2009), whereas significantly smaller islets with reduced β-cell mass are found in knockout mice. Thus, ANP might increase glucose uptake via stimulation of pancreatic insulin release.

Interestingly, ANP infusion in ten fasting, healthy young men slightly increased circulating glucose levels (Birkenfeld et al., 2005). This effect might be explained by the acute effect of ANP on lipid mobilization, acutely increasing the flux of fatty acids to metabolic, insulin responsive organs and thereby inducing insulin resistance (Nowotny et al., 2013; Birkenfeld & Shulman, 2014), an effect that can be outbalanced in the long-term by increased usage of these fatty acids in β-oxidation. The notion that lipid mobilization enhances the distribution of fatty acids to ectopic organs inducing insulin resistance, is supported by the fact that short-term infusion of BNP, in a manner not increasing fatty acid levels, lowered circulating glucose concentrations slightly during the initial phase of an intravenous glucose tolerance test, together with reduced insulin secretion. In this case, the effect could be mediated by the increase in peripheral vasodilation (Heinisch et al., 2012) and through improved glucose transport across the capillary wall into the interstitial space (Jensen et al., 1998). Together, these studies suggest that NP might enhance insulin-stimulated glucose disposition. Whether or not NPs directly affect insulin signaling deserves to be studied in more detail.

Hepatic and skeletal muscle lipid content is strongly associated with insulin resistance (Samuel & Shulman, 2012; Birkenfeld & Shulman, 2014). In liver and skeletal muscle, insulin resistance develops when there is an imbalance between supply and utilization of intracellular lipid leading to net accumulation of bioactive lipid species, such as intracellular diacylglycerol (DAG hypothesis) (Birkenfeld & Shulman, 2014). In obesity and metabolic syndrome, this lipid accumulation is primarily achieved by excessive caloric intake exceeding the capacity of hepatocytes and myocytes to metabolize or export fatty acids while refining or uncoupling mitochondrial respiration and enhancing lipid

oxidation have been shown to improve insulin sensitivity (Lee et al., 2010; Thielecke et al., 2010; Birkenfeld et al., 2011b, 2011c; Kumashiro et al., 2013; Perry et al., 2013; Neuschafer-Rube et al., 2014).

NPs could ameliorate lipid-induced insulin resistance through improvements in hepatic (Birkenfeld et al., 2008) and muscular (Engeli et al., 2012) lipid oxidation. In line with the notion, NPs preserve mitochondrial function and insulin sensitivity in high fat feeding in mice (Miyashita et al., 2009). Cross sectional studies support the hypothesis that NPs protect from the development of T2D and are explained in detail below. Investigation of the effect of BNP on insulin sensitivity in individuals with impaired glucose tolerance or frank diabetes would be of interest now that data on healthy participants are available.

4.6. Natriuretic peptides in food intake and satiety

As mentioned above, NPRB, the CNP receptor, is predominantly found in the brain. Therefore it has been suggested that CNP might play a role in the central regulation of energy metabolism and food intake. The hypothesis is supported by a recent study testing intracerebroventricular application of different CNP variants in mice. The intervention substantially decreased food intake after a 48 h-fast and nocturnal food intake, whereas intraperitoneal CNP injection did not alter feeding behavior. Anorexigenic effects of CNP are evoked by melanocortin system activation as well as suppression of orexigenic mediators such as ghrelin and neuropeptide Y (NPY) (Yamada-Goto et al., 2013). In human subjects, short-term BNP infusion suppress hunger, perhaps by decreasing total and acetylated ghrelin concentrations (Vila et al., 2012). However, regulation of food intake is complex and NP influence on hunger and satiety is a still emerging research field. To date, it is unknown whether BNP's anorexigenic effects are mediated by stimulation of hypothalamic AMP-activated protein kinase (AMPK) through ghrelin, or another regulator of hypothalamic AMPK activity. Insulin, glucose and certain fatty acids might be involved in the regulation of satiety through BNP (Jens Jordan & Birkenfeld, 2012). Additionally, high BNP levels are associated with suppressed levels of the anorexigenic adipokine leptin in heart failure patients, suggesting a regulatory effect of the NP system on leptin release. An increase in food intake may ensue (Melenovsky et al., 2013). Clearly, the effect of NP on leptin release warrants careful clinical studies to better understand the importance of NP on adipokines such as leptin.

A summary of the metabolic actions and phenotypes of NP animal models and human polymorphisms is given in Table 1.

5. Natriuretic peptides in human cardiometabolic disease

5.1. Natriuretic peptides in obesity

During the last years, numerous studies demonstrated an inverse relationship between circulating NP levels and bodyweight (Wang et al., 2004; Das et al., 2005; Olsen et al., 2005; Sugisawa et al., 2010; Khan et al., 2011; Cannone et al., 2013). This correlation can also be observed in chronic heart failure patients, despite increased NP levels, due to cardiac wall stress (Stavrakis et al., 2013).

Increased NP levels due to a genetic C(−55)A polymorphism of the NPRC are associated with lower prevalence of obesity and abdominal adiposity compared to individuals with intact NPRC (Sarzani et al., 2004). Another genetic polymorphism, in the ANP-promoter region, is associated with higher ANP levels and a favorable cardiometabolic phenotype including lower BMI and blood pressure as well as lower prevalence of obesity and metabolic syndrome (Newton-Cheh et al., 2009; Cannone et al., 2011; Arora et al., 2013; Cannone et al., 2013).

However, some studies show discordant results, indicating that there is no or even a positive correlation between BMI and systemic NP concentrations (Grandi et al., 2004; Abdulle et al., 2007). Elevated

Table 1
Metabolic phenotypes.

Genetic variation	NP related effect	Phenotype	Publication
NPRC−/− mice	↑ ANP	↑ bone metabolism, delayed enchondral ossification ↑ long bone growth ↓ blood pressure ↑ urine excretion ↓ WAT mass ↑ energy expenditure	Jaubert et al., 1999 Matsukawa et al., 1999 Bordicchia et al., 2012
BNP-Tg mice	↑ BNP	↓ body weight ↓ visceral and subcutaneous fat mass ↓ diet-induced ectopic fat accumulation ↑ glucose tolerance ↑ muscle mitochondrial content ↑ lipid oxidation rate	Miyashita et al., 2009
cGK-Tg mice	↑ cGMP	↓ body weight ↓ visceral and subcutaneous fat mass ↓ diet-induced ectopic fat accumulation ↑ glucose tolerance ↑ muscle mitochondrial content ↑ lipid oxidation rate	Miyashita et al., 2009
GC-A+/− mice	↓ cGMP-signaling	↑ body weight ↑ fat mass ↓ glucose tolerance	Miyashita et al., 2009
BNP promoter T-381C polymorphism (humans)	↑ BNP	↓ blood glucose levels ↓ T2DM-risk	Meirhaeghe et al., 2007 Choquet et al., 2009
rs5068 (humans)	↑ ANP = BNP	↓ blood pressure ↓ BMI and prevalence of obesity	Newton-Cheh et al., 2009 Arora et al., 2013 Cannone et al., 2011, 2013
NPRC polymorphism C(−55)A	↑ ANP	↓ blood pressure ↓ BMI and prevalence of obesity	Sarzani et al., 1999, 2004
Neprilysin−/− mice		↑ body weight ↑ insulin resistance ↓ HDL, ↑ VLDL	Becker et al., 2010

Correlations between natriuretic peptide system related genetic and cardiometabolic phenotypes Tg transgenic; cGK cGMP dependent protein kinase G; GC-A guanylyl-cyclase; WAT white adipose tissue; T2DM type 2 diabetes mellitus; HDL high-density lipoprotein; VLDL very low- density lipoprotein ↑ increase; ↓ decrease; = no change.

NT-proBNP levels comparable to heart failure patients with NYHA-stage I have been reported in morbidly obese patients (BMI > 40 kg/m^2). However, the authors relate their findings to the enormous cardiac burden secondary to morbid obesity (Hermann-Arnhof et al., 2005). Yet, it is widely agreed that obesity is a state of a NP deficiency. Differences in sample handling and analytical techniques could contribute to the variability (Buckley et al., 1999; Nowatzke & Cole, 2003; Belenky et al., 2004).

In lean, healthy subjects cardiac NP deficiency release is acutely enhanced by physical exercise (Moro et al., 2004a; Scharhag et al., 2005; Frassl et al., 2008; Knebel et al., 2009; Tian et al., 2012; Baker et al., 2013). In marathon runners NT-proBNP increased directly after the run while BNP showed a delayed reaction (Frassl et al., 2008). Interestingly both hormones show a sustained increase during the first 24 h after prolonged running with a delayed return to basal levels more than 24 h after the run (Frassl et al., 2008; Tian et al., 2012).

In contrast to lean subjects, circulating NP levels are suppressed and acute NP responses are blunted in obese individuals (Koppo et al., 2010) but can be restored by long-term physical training (C. Moro et al., 2005; Chen-Tournoux et al., 2010; Changchien et al., 2011; Abrahamsson et al., 2013; Martin et al., 2013). Investigation of a total of 7770 subjects who participated in the Framingham Heart Study and the Malmö Diabetes and Cancer Study revealed that obesity and insulin resistance are associated with markedly reduced plasma NP levels (Khan et al., 2011). Clinically relevant hypercortisolism comes along with central adiposity and the full range of metabolic syndrome symptoms. Despite the metabolic phenotype, NP levels seem to be increased in subjects with hypercortisolism (Yamaji et al., 1988; Tabarin et al., 1990). Elevated NP levels might be attributed to cardiovascular diseases, a major determinant of mortality in hypercortisolism (Mancini et al., 2004; Toja et al., 2012; Shibusawa et al., 2013). Interestingly, NP response appears to be blunted in hypercortisolism, despite elevated NP levels (Sala et al., 2001). However, the role of NP in clinically relevant hypercortisolism is still a controversial issue and alterations in NP receptor distribution and signaling due to hypercortisolism deserve further investigation.

So far, several potential reasons for the relative NP deficiency in human metabolic disease have been considered. Increased NP degradation could be one possible cause of decreased NP plasma levels in obese individuals. As mentioned before, natriuretic peptides are cleared by neutral endopeptidase neprilysin and NPRC (Maack et al., 1987; Kenny et al., 1993). NPRA and NPRC have been identified in human adipose tissue in abundance, implying that adipose tissue is not just a target organ for NP but also maintains a regulatory influence on circulating NP levels (Sarzani et al., 1996; Nakatsuji et al., 2010; Pivovarova et al., 2012). NPRC is increased in adipose tissue of obese hypertensive patients compared to non-obese and normotensive individuals (Dessi-Fulgheri et al., 1997). Moreover; hyperinsulinemia induces NPRC expression in human adipocytes (Nakatsuji et al., 2010) and monocytes (Pivovarova et al., 2012). Additionally, neprilysin, the NP degrading endopeptidase, is expressed in human adipose tissue and at increased levels in obesity (Standeven et al., 2011). Taken together these findings militate for an accelerated NP clearance due to a shift in the NPRA/NPRC ratio towards NPRC and increased neprilysin levels in human metabolic disease, emerging to a vicious cycle of NP suppression, obesity and insulin resistance (Fig. 4).

In line with the notion, caloric restriction and weight loss can restore BNP levels in humans (Chainani-Wu et al., 2010) and NP signaling in rodents by decreasing adipose tissue NPRC expression (Sarzani et al., 1995). This effect might in part be attributed to reduced hyperinsulinemia (Chainani-Wu et al., 2010).

Apart from their general association with lower body fat mass, NPs may favorably affect adipose tissue distribution. Increased NP levels are associated with reductions in visceral adipose tissue (VAT) and in ectopic, intra-organ fat deposition such as intrahepatic lipid accumulation (Sarzani et al., 2004; Cheng et al., 2011; Neeland et al., 2013). One possible explanation is increased susceptibility to NP mediated lipolysis in VAT due to increased NP receptor expression in VAT compared to

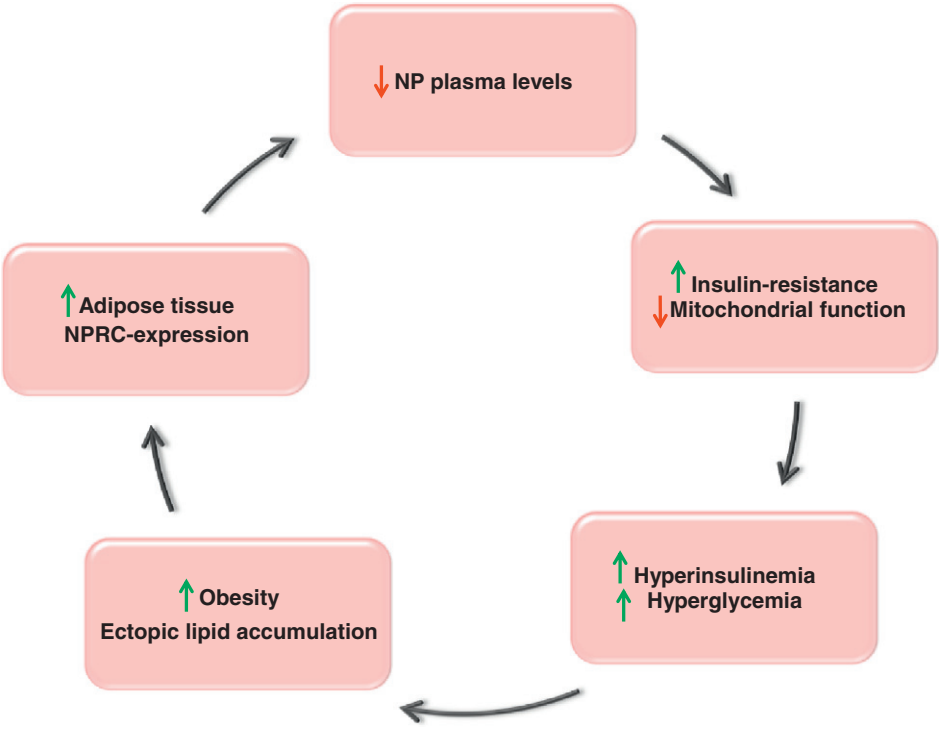

Fig. 4. Obesity is associated with impaired NP release and increased expression of the NP degrading receptor NPRC, leading to a significant reduction of systemic NP levels. NP deficiency contributes to insulin resistance and mitochondrial dysfunction which in turn lead to hyperglycemia and increased insulin levels resulting in further weight gain. Thus, obesity, insulin resistance and natriuretic peptide deficiency emerge to a viscous cycle.

subcutaneous adipose tissue (SAT) (Pivovarova et al., 2012). Another possible explanation is that SAT generally exhibits less lipolytic activity than VAT (Arner, 1995).

There are also indications of an impaired cardiac NP release in metabolic diseases. In obese individuals, reduced saline load-induced NP responses were observed as early as 20 years ago (Licata et al., 1994). More recently, a number of studies demonstrated that circulating levels of NT-proANP and NT-proBNP are reduced in obesity, too. As mentioned above, NT-proANP and NT-proBNP are side-products of NP release. These peptides are cleaved of the amino-terminus of the inactive prohormones to produce biologically active ANP and BNP (Yan et al., 2000). The aminoterminal cleavage products of ANP and BNP are structurally distinct from the biologically active peptides making NPRC mediated degradation unlikely (Minami et al., 2004; Das et al., 2005). Mizuno et al. recently observed that differences between BNP levels measured in the aortic root and BNP levels in the coronary sinus are negatively correlated with BMI, supporting the hypothesis of an impaired myocardial NP release in obese individuals (Mizuno et al., 2013). Others observed correlations between NP plasma levels and lean body mass rather than fat mass (Das et al., 2005; Asferg et al., 2013a, 2013b). Interestingly; lower NP levels were strongly related to high glucose and insulin levels independent of body composition and adipose tissue distribution (Asferg et al., 2013a, 2013b).

5.2. Natriuretic peptides in insulin resistance and diabetes

A potential connection between plasma glucose and insulin levels and the natriuretic peptide system has been observed in several studies. Acute hyperglycemia induces a rapid rise of ANP levels in response to hyperglycemia induced sodium and fluid retention (Clark et al., 1993; Böhlen et al., 1994; McKenna et al., 2000). On the other hand, low BNP levels are associated with insulin resistance and type 2 diabetes (T2D) (Kroon et al., 2012). This correlation can be partially explained by the association of T2D and obesity. However; statistical correction for BMI does not abolish the correlation between NP-levels and diabetes onset. Data from the Women's Health Study revealed that individuals with NT-proBNP levels near the upper limit of normal have significantly lower incidence of diabetes (Everett et al., 2013).

Large cross-sectional studies confirm the relationship between low NP concentrations and high glucose and insulin levels, as well as high plasma cholesterol and triglyceride concentrations (Olsen et al., 2005; Wang et al., 2007). Data from a total of 7770 participants in the Framingham Heart Study and the Malmö Diet and Cancer Study revealed that lower NP levels are associated with higher susceptibility to insulin resistance in both lean and obese individuals (Khan et al., 2011). Moreover, in the cohort of the longitudinal Malmö Diet and Cancer Study low NP concentrations were clearly predictive of new-onset diabetes as well as blood glucose level progression over the study period (Magnusson et al., 2012). Correspondingly, increased NP levels seem to be protective against insulin resistance (Neeland et al., 2013) and T2D (Pfister et al., 2011; Cannone et al., 2013; Everett et al., 2013). Along these lines, Heinisch et al. observed that BNP infusion during intravenous glucose tolerance testing lowers blood glucose concentrations transiently by increasing glucose distribution volume in healthy men (Heinisch et al., 2012). These findings suggest that NPs might be protective against T2D due to a direct, insulin-independent antihyperglycemic effect, and by increasing lipid oxidation rates and pertaining mitochondrial function as outlined before. Vice versa, NP deficiency contributes and aggravates at least in part metabolic disease, such as insulin resistance and diabetes on the long run.

Another interesting link has recently been discovered between glucagon-like peptide-1 receptor (GLP-1R) agonists and natriuretic peptide release. GLP-1R agonists are a group of antidiabetic drugs that enhance insulin secretion and suppress glucagon release (Drucker & Nauck, 2006). In addition, GLP-1 receptor agonists promote satiety and weight loss while decreasing blood pressure (Ussher & Drucker, 2012). Heart rate tends to increase with GLP-1R agonist treatment. The mechanism of the cardiovascular side effects is still incompletely understood. However, Kim et al. recently demonstrated that the GLP-1R agonist liraglutide induces cardiac ANP release in mice, leading to enhanced natriuresis and vasodilatation (Kim et al., 2013). An increase in heart rate could, hence, be a compensatory response.

5.3. Natriuretic peptides in cardiovascular diseases

Another facet of metabolic diseases is the link between obesity and arterial hypertension. Obese individuals have a two- to threefold higher prevalence of arterial hypertension compared to lean subjects (Stamler et al., 1978). Although many aspects of obesity related arterial hypertension have been intensively studied during the last years, not all mechanisms are well understood (Aneja et al., 2004; Jordan & Engeli, 2012). In lean healthy individuals, administration of sodium load or vasopressors induces myocardial NP release and consequently enhances natriuresis (Uehlinger et al., 1987; Clinkingbeard et al., 1990; Bruun et al., 2000; Park et al., 2013). The response is impaired in obese individuals (Asferg et al., 2013a, 2013b). Possibly, obesity promotes hypertension partly through reduced direct vascular and renal NP responses as well as impaired NP-mediated RAAS inhibition (Burnett et al., 1984; Shi et al., 2001). NP deficiency might contribute to the development of obesity related hypertension directly through reduced vasodilatation (Protter et al., 1996; van der Zander et al., 1999) and enhanced sodium and water reabsorption (Sonnenberg et al., 1986; Harris et al., 1987; Yoshimura et al., 1991), as well as decreased suppression of the renin–angiotensin–aldosterone-system (RAAS). All of these mechanisms are considered major contributing factors in obese, hypertensive patients (Kurukulasuriya et al., 2011).

Moreover, enhanced sympathetic nervous system activity has been implied in the development of obesity related arterial hypertension. NP have been shown to attenuate muscle sympathetic nerve activity (Floras, 1990, 1995), in part by blocking ganglionic neurotransmission (Floras, 1995), thereby attenuating the reflex sympathetic response to baroreceptor deactivation (Floras, 1990). Brunner-La Rocca et al. demonstrated an inhibitory effect on systemic and cardiac sympathetic nervous system activity for BNP at physiological levels (Brunner-La Rocca et al., 2001). Thus, insufficient NP-response might contribute to enhanced sympathetic nervous system activity in the setting of obesity.

Ethnic differences have been reported in the prevalence of cardiometabolic disease, with a higher prevalence in subjects with African (Taylor et al., 2010; Liu et al., 2013) or Hispanic ancestry (Guzman, 2012) compared to Caucasians. The reasons for these ethnic variances remain elusive. Lifestyle and socioeconomic status are considered to play a major role, however; interracial differences are preserved in Africans and Caucasians with comparable socioeconomic status (Sampson et al., 2014). One possible mechanism might be the inadequately higher RAAS-activity in individuals of African origin (Flack et al., 2010). Interestingly, significant ethnic differences were also found in NT-proBNP levels with the highest levels found in non-Hispanic whites, followed by Hispanics, Chinese and African-Americans in decreasing order (Choi et al., 2012). Due to their metabolic effects and modulatory impact on RAAS activity (Burnett et al., 1984; Johnson et al., 1988; Shi et al., 2001), it seems intriguing to speculate that ethnic differences in developing hypertension and metabolic disease might in part be mediated by variances in circulating NP levels and the resulting change in modulation of the RAAS. However, the issue is still poorly understood and further investigation is needed to elucidate the meaning of interracial differences in the NP system.

Apart from their impact on blood pressure regulation, NPs also seem to have a beneficial effect cardiac remodeling in essential hypertension, reducing left ventricular hypertrophy (LVH) (Rubattu et al., 2006). Conversely, conditions associated with NP deficiency result in an increased risk for cardiac hypertrophy in hypertensive patients. Rubattu et al. demonstrated that hypertensive patients with metabolic syndrome

have lower ANP and NT-proBNP levels, higher cardiac mass and higher prevalence of LV hypertrophy compared to hypertensive subjects without metabolic syndrome (Rubattu et al., 2007).

All in all, these findings suggest that lower NP levels are associated with obesity and increased risk of metabolic and cardiovascular disease, while higher NP levels come along with a more favorable cardiometabolic phenotype.

5.4. Natriuretic peptides in heart failure and cardiac cachexia

Severe chronic heart failure (CHF) is associated with metabolic alterations and cardiac cachexia. A number of immunological and neurohormonal processes are involved in the genesis of heart failure-induced cachexia, reviewed in (von Haehling et al., 2007; Martins et al., 2013). The pathophysiology of cardiac cachexia is multifactorial, resulting from several factors interacting in a complex system with metabolic, immune and neurohormonal consequences, probably triggered to protect the heart from damage (Martins et al., 2013). Systemic NP levels are elevated in CHF due to cardiac wall stress resulting from increased end diastolic pressure. BNP and NT-proBNP have been well established as diagnostic and prognostic markers for heart failure patients (Cowie et al., 2003; Rothenburger et al., 2004; Januzzi et al., 2005; Fonarow et al., 2007). With respect to their lipolytic properties and activation of oxidative metabolism natriuretic peptides might contribute to weight loss and cachexia in heart failure (McCord et al., 2004; McEntegart et al., 2007; Polak et al., 2011) and evidence has been given in numerous studies that high NP levels are associated with cardiac cachexia (Horwich et al., 2001; Lavie et al., 2003; Melenovsky et al., 2013; Stavrakis et al., 2013). However, through improvements in muscular oxidative function, NP could also counteract the muscle fiber type switch in heart failure patients. Patients with chronic heart failure feature relative reductions in oxidative type 1 muscle fibers, which further limits aerobic exercise capacity.

These mechanisms are only plausible when NP mediated metabolic responses do not desensitize due to chronic NP excess in heart failure. We have addressed the question whether or not the ex vivo lipolytic response to ANP is attenuated in isolated adipocytes from patients with severely impaired left ventricular function in part through changes in the NP receptor expression. We observed that the adipose tissue NP system does not desensitize in heart failure patients, as evidenced by a preserved lipolytic response to ANP (Birkenfeld et al., 2011a). The finding has been confirmed in different clinical settings (Polak et al., 2011; Szabo et al., 2013). Whether metabolic responses to NP are also preserved in skeletal muscle is unknown.

6. Therapeutic potential of natriuretic peptides in metabolic syndrome and its components

6.1. Cardiovascular disease

Recombinant NP analogs such as Carperitide (synthetic ANP) or Nesiritide (synthetic BNP) have been approved for intravenous treatment of acutely decompensated heart failure in Japan and the US. However, the short plasma half life (Astrup et al., 1985), the need for intravenous or subcutaneous infusion, and adverse events such as relevant hypotension requiring drug discontinuation limit the clinical utility (Suwa et al., 2005; Suzuki et al., 2013).

In the past, the recombinant BNP analog Nesiritide was widely used for the treatment of acute decompensated heart failure in the US. However, standard dose Nesiritide treatment increased mortality and worsened renal function (Sackner-Bernstein et al., 2005a, 2005b). Thus far, there is no evidence for a significant benefit of Nesiritide treatment in heart failure from placebo-controlled clinical trials (Yancy et al., 2008; O'Connor et al., 2011; Topol, 2011). Perhaps, Nesiritide may have a neutral or even protective influence on renal function when applied in non-hypotensive doses (Chen et al., 2007; Mentzer et al., 2007; Witteles et al., 2007). In patients with congestive heart failure and reduced renal function, the effect seems to be neutral (H.H. Chen et al., 2013).

More recently, Nesiritide has been tested in pulmonary hypertension patients. Nesiritide infusion reduced pulmonary artery and right ventricular pressures in these patients (Michaels et al., 2005; T. Chen et al., 2013).

Another option to augment the NP system is to block NP clearance. In animal models inhibition of the NP degrading neutral endopeptidase neprilysin increased NP plasma levels and promoted diuresis (Good et al., 1995). In clinical trials, monotherapy with neutral endopeptidase inhibitors showed poor results, so far. Acute and chronic effects on cardiac output, vascular tone and blood pressure were minor (Northridge et al., 1989; Bevan et al., 1992). Although neprilysin inhibitors in general are well tolerated, long-term treatment with high doses of certain neprilysin inhibitors, was associated with severe adverse events such as severe aplastic anemia and angioedema (Cleland & Swedberg, 1998).

Combined neprilysin and RAAS inhibition may overcome the limited efficacy of neprilysin inhibitor monotherapy but is not without risks. Recent in vivo data from animal models indicate that dual inhibition of the RAAS and augmentation of the NP system might decelerate tachycardia-induced left ventricular hypertrophy and chronic heart failure progression (Birner et al., 2012). Yet, the dual vasopeptidase inhibitor Omapatrilat that blocked ACE and neprilysin had to be withdrawn from the market owing to an excessive angioedema risk. More recently, a large scale trial with 1328 mild to moderately hypertensive patients confirmed that dual inhibition of angiotensin II subtype 1 receptors and neprilysin with LCZ696 decreases blood pressure more than angiotensin II subtype 1 receptor blockade alone (Ruilope et al., 2010). LCZ696 is an unusual compound comprised of the angiotensin II subtype 1 receptor blocker Valsartan tied to a neprilysin inhibitor through an ester bond. The combination is in late stage clinical development for the treatment of heart failure and arterial hypertension.

Besides direct NP agonistic or augmenting strategies, other pharmacological strategies yield at downstream mediators of the NPRA dependent pathway. Phosphodiesterase 5 (PDE5) inhibition selectively blocks cyclic GMP degradation (Omori & Kotera, 2007), NPRA's and NPRB's second messenger (Waldman et al., 1984; Song et al., 1988). So far, phosphodiesterase inhibitors have been approved for the treatment of pulmonary hypertension (Galiè et al., 2009) as well as demand actuated medication for the treatment of erectile dysfunction. In general, PDE5-inhibitors are well tolerated when contraindications such as use of nitrates in coronary heart disease are heeded (Bruzziches et al., 2013). Sildenafil is a highly selective PDE-5 inhibitor augmenting cGMP signaling (Glossmann et al., 1999). Sildenafil treatment may slow down disease progression in early, asymptomatic diabetic cardiomyopathy (Giannetta et al., 2012) and improve left ventricular function in heart failure (Guazzi et al., 2011).

Novel strategies exploiting desirable cardiovascular effects of NPs for the prevention and treatment of cardiovascular diseases are a matter of ongoing preclinical and clinical research. Thus far, the ideal way to clinically manipulate the NP system has not been found.

6.2. Metabolic disease

The notion that NP could be used as a therapeutic strategy in obesity, the metabolic syndrome, or T2D has been recently entertained (Costello-Boerrigter, 2013). Indeed, by improving lipid mobilization, oxidative metabolism, and blood pressure, NPs address a root cause of these disorders. Regular physical training can restore circulating NP concentrations and NP effectiveness in obese individuals (Moro et al., 2005) in addition to the known beneficial effects on improving weight loss, insulin sensitivity, and cardiovascular risk (Goodpaster et al., 2003; Houmard et al., 2004). Endurance training also improves skeletal muscle oxidative capacity (Pruchnic et al., 2004). Recent experimental data suggest that the positive effects of physical training are at least in part caused by exercise-induced NP elevation in rodents and humans

(Mitsuishi et al., 2008; Engeli et al., 2012). As mentioned above, in a murine model, increased BNP levels were protective against diet induced obesity and insulin resistance (Miyashita et al., 2009) and large cross sectional studies confirm these data in human subjects (Sarzani et al., 2004). Moreover, higher NP levels were also associated with a more favorable lipid profile comprising lower circulating LDL and higher HDL concentrations (Pervanidou et al., 2009; Wang et al., 2013). These findings suggest that NPs might be protective against dyslipidemia, which conveys increased cardiovascular risk in obesity and T2D.

Dual ACE and neprilysin inhibition improved insulin sensitivity in diabetic rats (Wang et al., 2003). The authors related the effect to increased bradykinin levels and stimulation of the bradykinin receptor B_2. Regrettably, natriuretic peptide levels were not measured. Also, other dual vasopeptidase inhibitors may improve microvascular circulation including endoneurial blood flow, which is important in the pathogenesis of diabetic polyneuropathy (Davidson et al., 2007; Oltman et al., 2009).

Downstream mediators of the NPRA pathway may also provide treatment targets. Natriuretic peptides are considered to facilitate their metabolic effects mainly via cGMP dependent GK-I activation. (Sengenès et al., 2003; Mitsuishi et al., 2008; Miyashita et al., 2009). Thus, activation of GK-I by other means is likely to have a similar impact on energy homeostasis (Miyashita et al., 2009; Mitschke et al., 2013). A well-known pharmacological target is phosphodiesterase-5 that degrades cyclic GMP. In murine models, long-term treatment with the PDE-5 inhibitor Sildenafil improves skeletal muscle metabolic index, diet-induced insulin resistance and weight-gain (Ayala et al., 2007; Rizzo et al., 2010; Handa et al., 2013). These findings are consistent with the idea that augmented cGMP signaling rescues mitochondrial function and promotes mitochondrial biogenesis.

Given their effects on mitochondrial metabolism, on lipid and glucose metabolism, and on arterial blood pressure, NPs provide a particularly promising target for the treatment of obesity and its related diseases. To date, many anti-obesity drugs were withdrawn from the market due to their unfavorable cardiovascular profile. In contrast, NP system manipulation is a promising approach to simultaneously address common cardiovascular and metabolic conditions.

7. Novel pharmacologic approaches

New strategies are needed to make the NP amenable for more chronic treatments. CD-NP is a novel, chimeric NP analog that is ligand to both natriuretic peptide receptors A and B and is more resistant to proteolytic degradation compared to ANP and BNP. CD-NP is a fusion product of CNP and the carboxyterminus of dendroaspis natriuretic peptide (DNP) from the venom of the green mamba snake. Due to its DNP-carboxyterminal tail CD-NP has a 13-, 4-, and threefold increased half-life compared to ANP, BNP and CNP respectively (Dickey & Potter, 2011). CD-NP was designed to generate a peptide that combines "the cardiac unloading, antiproliferative, antifibrotic, and minimal hypotensive properties of CNP with the renal-enhancing actions of DNP" (McKie et al., 2010) and minimal adverse side effects. First data in humans confirms significant natriuretic and diuretic effects as well as RAAS suppressing properties with only slight changes in arterial blood pressure (Lee et al., 2009). Recently, long-term subcutaneous treatment with CD-NP was found to significantly attenuate left ventricular fibrosis in rats with unilateral nephrectomy-induced cardiac fibrosis (Martin et al., 2013). Current approaches yield at CD-NP-eluting patches that can be applied locally for the treatment of localized myocardial fibrosis, as for example after myocardial infarction (Ng et al., 2013).

Another novel natriuretic peptide receptor-A (NPR-A) agonist PL-3994 (Hept-cyclo(Cys-His-Phe-d-Ala-Gly-Arg-d-Nle-Asp-Arg-Ile-Ser-Cys)-Tyr-[Arg mimetic]-NH(2)), has been designed and proven high affinity to NPRA. PL-3994 induces a sustained cGMP generation in NPRAs. Interestingly, PL-3994 has been reported to be resistant to degradation by human neutral endopeptidase. Thus, PL-3994 might have a profile predictive of longer clinical activity than other related peptides (Edelson et al., 2013).

Pegylation, the covalent binding of poly(ethylene glycol) (PEG) to peptides and proteins, is another approach to prolong substance release and to delay degradation (Roberts et al., 2002; Veronese & Pasut, 2005; Werle & Bernkop-Schnürch, 2006). Nesher et al. reversibly pegylated ANP and thereby achieved prolonged elevation of ANP plasma levels and blood pressure reduction in hypertensive rats (Nesher et al., 2007). More recently; ANP has been fused to the Fc-domain of immunoglobulin G (IgG) reaching plasma half-times approximately 2 orders of magnitude longer than unfused ANP (Mezo et al., 2012). However, Fc-ANP was significantly weaker than the unconjugated peptide.

Recently, the Wang lab described miRNA-425 (miR-425) as a novel negative regulator of ANP expression. miR-425 is expressed in human atria and ventricles and silenced NPPA mRNA in an allele-specific manner (Arora et al., 2013). Possibly, miR-425 antagonists could be designed to increase ANP levels in order to treat disorders of salt overload, including hypertension and heart failure and metabolic disease.

8. Conclusion

Natriuretic peptides are well known for their renal and cardiovascular effects. They are widely used as prognostic biomarkers in heart failure and a number of therapeutic strategies aim to exploit the hypotensive, natriuretic and antihypertrophic properties of the NP system. Metabolic and cardiovascular diseases are closely linked and constitute a major public health issue in industrialized countries. A growing body of evidence indicates that NPs might be a crucial piece of the puzzle linking the heart to energy metabolism. In paradigm, the heart can be regarded a sensor chaperoning whole body lipid and glucose metabolism. Connecting cardiovascular and energy metabolism, the NP system provides a bouquet of options for pharmacological intervention. To date, recombinant peptides and inhibitors of the degradation process of NP are the most promising molecules in this regard. Moreover, mi-RNA 425 has recently been shown to be a regulator of ANP and as such, might be a suitable target to increase ANP concentrations. Time will show, if it will be possible to treat cardiometabolic diseases with NP mimetic molecules.

Conflict of interest

We do not have any actual or potential conflict of interest including any financial, personal or other relationships with individuals or organizations within three years of initiating the work that could inappropriately influence, or be perceived to influence, the study design or data Interpretation of our work.

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