Mol Cell Biochem (2010) 334:53–65
DOI 10.1007/s11010-009-0326-8

Central role of guanylyl cyclase in natriuretic peptide signaling in hypertension and metabolic syndrome

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Received: 13 March 2009 / Accepted: 4 November 2009 / Published online: 25 November 2009
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Abstract Studied for nearly 30 years for its ability to control many parameters, such as vascular smooth muscle cell relaxation, heart fibrosis, and kidney function, the natriuretic peptide (NP) system is now considered to be a key element in several other major metabolic pathways. After stimulation by NPs, natriuretic peptide receptors (NPR) convert GTP to the second messenger cGMP. In addition to its vasodilatory effects and natriuretic and diuretic functions, cGMP has been positively associated with fat cell function, apoptosis, and NPR expression/activity modulation. The NP system is also closely linked to metabolic syndrome (MetS) progression and obesity control. A new era is now on its way targeting the NP system to not only treat high blood pressure, but to also assist in the fight against the obesity pandemic. Here, we summarize recent data on the role of NPs in hypertension and MetS.

Keywords Natriuretic peptides · cGMP · Hypertension · Metabolic syndrome · Obesity

Introduction: natriuretic peptide receptors/guanylyl cyclase signaling

Since the discovery of atrial natriuretic peptide (ANP) way back in 1981 [1], particulate guanylyl cyclase (GC) signaling became a major field of interest for many groups [2–20]. After i.v. injection of atrial homogenates into rats, the active compound extracted from the atria was found to be a short peptide able to rapidly lower blood pressure (BP) and promote sodium and water excretion through a cGMP signaling pathway [11]. Since then, the mammalian natriuretic peptide (NP) family has acquired two additional members, B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), both originally identified in the porcine brain [15, 16]. These three NPs share a similar structure consisting of a 17-amino acid ring joined by a disulfide bridge. In humans, active ANP is a 28-amino-acid long peptide, whereas BNP and CNP are, respectively, 32 and 22 amino acids long. ANP is mainly produced in the atria and stored in granules as a 126-amino-acid proANP form. ProANP secretion is stimulated by atrial stretching after volume overload, and active ANP is produced under the action of corin, a transmembrane serine protease acting as a converting enzyme [7, 20]. ANP in circulation targets several organs, including the heart, kidney, adrenal, lung, vascular smooth muscle, and adipose tissue. BNP, which acts on the same organs, is also produced in the heart as a 134-amino-acid long preproBNP. Regulated by the transcription factor GATA-4, BNP is actively produced by the ventricles upon atrial wall stretching [10, 18]. In contrast to ANP and BNP, CNP acts in an autocrine/paracrine manner and is secreted by the vascular endothelium to control vascular tonus and endothelium growth [6]. ANP and BNP genes are both located on human chromosome 1 at the 1p36.3 locus, whereas CNP gene is located on chromosome 2 between 2q24 and the 2q terminus. In mice, ANP and BNP genes are both located on chromosome 4 (4E2), while CNP gene is positioned at the chromosome 1D locus. Rat ANP, BNP, and CNP genes are found on chromosomes 5q35, 5q36, and 9q35, respectively. The similar structure

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of the NPs suggests a common ancestor gene, and it has been proposed that CNP gene generated ANP and BNP genes through gene duplication [17].

Receptors for these peptides, called natriuretic peptide receptors (NPR), are composed of three members: NPRA, NPRB, and NPRC. NPRA and NPRB possess enzymatic activity required for signal transduction. Also known as guanylyl cyclase A and B (GCA and GCB), these two receptors are structurally similar, and each monomer is composed of a large extracellular ligand-binding domain, a single transmembrane domain followed by a kinase homology domain (KHD), a coiled-coil dimerization domain, and a GC catalytic domain at its intracellular C-terminal end [8, 9, 14, 19]. NPRA, also named ANF-RGC for atrial natriuretic factor receptor guanylate cyclase, can bind the three NPs but with a marked preference for ANP and BNP over CNP while NPRB is activated preferentially by CNP [5]. NPRC is a non-GC receptor containing a very small intracellular domain 37 amino acids long [13]. Originally described as the clearance receptor for NPs, NPRC was also found to be coupled to the adenylyl cyclase/cAMP signal transduction system through inhibitory guanine nucleotide regulatory protein [2, 3, 12].

The activity of NPRA and NPRB is tightly regulated and, in the basal state, the conversion of GTP to cGMP by the GC domain is low. Activation of these receptors is triggered by the binding of NPs to the extracellular domain of a homo-oligomerized receptor, inducing conformational receptor change allowing ATP to bind to the KHD which relieves repression of the catalytic domain. Active GC is formed from two domains of the homodimer receptor which leads to cGMP production. This second messenger will ultimately transduce the initial NP signal by interacting with several target proteins, including protein kinase G (PKG), ion-gated channels, and phosphodiesterases (PDEs) [4]. These cGMP targets will be discussed further in the following sections.

Regulation of NPR expression and activity

Natriuretic peptide receptors expression and activity are regulated by several factors, including growth factors, angiotensin II, endothelin, glucocorticoids, and NPs themselves. Regulation of NPRA transcriptional activity is the most widely studied among the three NPRs. The human, mouse, and rat NPRA gene promoter, controlled by an inverted CCAAT box instead of the typical TATA box, is the basic element for recruiting transcription factors. The NPRA gene promoter contains several elements that up- or down-regulate the mRNA expression. Among these are the three Sp1-binding sites in the NPRA gene promoter, which drive transcriptional activity; mutation of one of the Sp1 sites reduces promoter activity by half whereas complete deletion of the three sites leads to a decrease in promoter activity of more than 90%. NPRA expression is increased by 12-fold when Ets-1 is overexpressed in mouse mesangial cells, while mutation of c-Ets-binding element completely abolishes this Ets-1-dependent induction [21]. One of the main differences in NPRA gene transcription between human, mouse, and rat species lies in the location of the transcription start site; indeed, the transcription start site in human NPRA gene is 88 base pairs upstream of the start codon, whereas in mice and rats this 5′untranslated region is, respectively, at 362 and 370 base pairs [22], suggesting a still unknown, species-specific mechanism of NPRA gene transcription. One of these mechanisms has been elucidated in rats. Indeed, the rat NPRA gene promoter contains a dinucleotide TA repetition, wherein the number of TA is inversely proportional to the NPRA expression level. Thus, even if the response to ANP is exaggerated in the rat model of essential hypertension, the spontaneously hypertensive rat (SHR), a longer TA repeat is associated with reduced NPRA mRNA levels compared to the normotensive Brown Norway (BN) strain [23, 24]. As anticipated, an intermediate number of TA repeats—between the 10 TA repeat segment of the BN strain and the 40 TA of SHR—results in an intermediate level of NPRA gene expression [23]. NPRA is controlled by a retro-inhibition loop involving the cGMP molecule as the main sensor. After stimulation by ANP, the NPRA gene promoter can down-regulate its own expression via a cGMP-dependent mechanism [25]. This down-regulation mechanism is under the control of a cis-regulatory element, called the cGMP response element (cGMP-RE), present in the NPRA gene promoter [26]. This DNA element is well defined in the human, mouse, and rat genomes but the *trans*-acting factors involved in sensitivity to cGMP are still unknown.

In addition to down-regulation mechanisms, desensitization, which affects the activity of the receptor rather than its expression level, is another means of tightly controlling NP action at the level of their receptors. The homologous desensitization mechanism has been shown to occur shortly after NP binding independently of cGMP accumulation [27]. After NP binding and receptor activation, the phosphorylation state of the KHD, located in the intracellular region of NPRA and NPRB, is rapidly reduced by the action of a protein phosphatase causing the dissociation of GC monomers and the diminution of GC activity. This mechanism of homologous desensitization has been documented for NPRA and NPRB. ANP-dependant modulation of NPRA activity and expression is summarized in Fig. 1. Protein kinase C (PKC) has been implicated in heterologous desensitization caused by factors other than NPs. Angiotensin II, lysophosphatidic acid, sphingosin-1-phosphate, platelet-derived growth factor (PDGF), basic fibroblast growth factor, and endothelin are among known factors

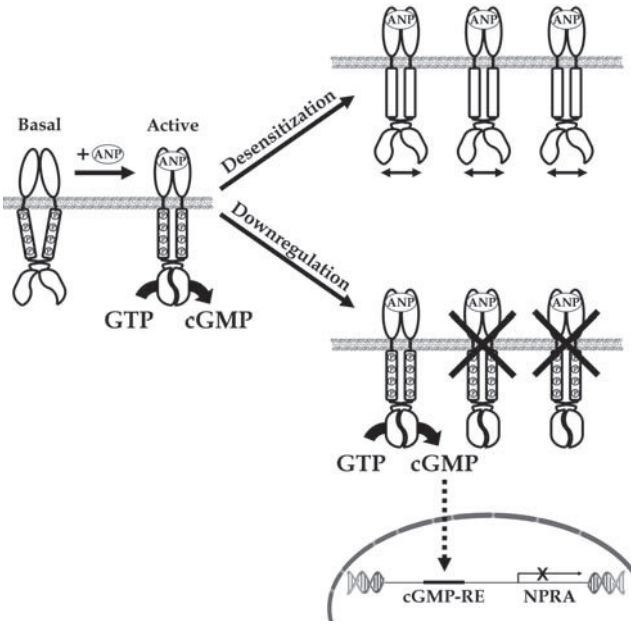

Fig. 1 ANP modulates NPRA activity and expression. The receptor exists in a basal state where the two catalytic subunits are separated from each other. After hormone binding, global rearrangement of all domains allows the cyclase to join and convert GTP to cGMP. Modulation of active receptors can occur in two distinct ways. The desensitization mechanism involves rapid dephosphorylation of the kinase domain which stops GTP conversion to cGMP without affecting receptor numbers. Chronic ANP stimulation causes receptor downregulation through the inhibition of gene transcription triggered by cGMP accumulation. Transcriptional inhibition is mediated by cGMP-RE and involves an unknown pathway

producing heterologous desensitization of NPRA and NPRB. These agents activate PKC, through diacylglycerol (DAG), resulting in dephosphorylation of specific phosphoserine and phosphothreonine sites on receptors that are different from those dephosphorylated by NP-induced desensitization [28]. In addition to PKC activation, NPRB desensitization can occur after inositol triphosphate (IP_3)-dependent elevation of intracellular calcium concentration [29]. Although the topology and signaling mechanisms of NPRB are well studied, its gene regulation is still poorly understood. The NPRB gene promoter is somewhat similar to that of NPRA; both are TATA-less, controlled by an inverted CCAAT-box, and contain several Sp1-binding sites. On the contrary, the NPRB promoter lacks the cGMP response element identified in NPRA, suggesting that the retro-inhibition loop for NPRB is different from that of NPRA in that it does not involve the same cis-element or that this type of retro-feedback does not exist for the CNP/NPRB/cGMP pathway.

The third receptor, NPRC, has been shown to be affected by various agents that modulate its expression levels. Indeed, stimulation of pulmonary arterial smooth muscle cells by fibroblast growth factors (FGF-1 and -2) and PDGF-BB has been demonstrated to reduce NPRC mRNA levels [30]. Moreover, treatment of vascular smooth muscle cells (VSMC) with noradrenaline, forskolin, sodium fluoride, and 8-bromo-cAMP has been associated with a decrease in the protein and mRNA levels of NPRC without affecting NPRA or NPRB [31]. Salt intake has also been found to lower NPRC mRNA levels in the kidneys independently of ANP and, again, with no effects on NPRA or NPRB content [32]. Although evidence of NPRC downregulation has been well documented, the exact signaling mechanisms are not fully understood and remain under investigation. A recent study [33] reported that an alternative spliced variant of NPRA, previously shown by us [34], to be ubiquitously expressed but at levels lower than 1%, causes deletion of 16 amino acids between Lys^{314} and Gln^{330} in the membrane-distal part of the extracellular domain, inhibiting ligand binding and receptor stimulation. This variant can form heterologous dimers with the wild-type receptor and interfere with its activity. It may represent another mechanism of reduced sensitivity to ANP [33].

Effects of post-GC signaling and cellular events

VSMC relaxation

Natriuretic peptide-dependent vasodilatation is probably the field that is most studied in cGMP signaling. It is well known that cGMP elevation leads to the relaxation of pre-contracted rat aortic rings [35–37]. VSMC contraction and relaxation are under the control of intracellular calcium spikes; anything affecting calcium concentration will shift the cells from a contractile to a resting state [38–40]. In brief, calcium induces contractions by activating calcium/calmodulin-dependent myosin light chain kinase which phosphorylates myosin light chain and activates myosin contractile adenosine triphosphatase (ATPase) [40–43]. ANP-dependent VSMC relaxation absolutely requires PKGI as PKGI-deficient mice do not respond to NPs or nitric oxide (NO) donors [44]. cGMP-dependent relaxation is observed after PKGI activation and subsequent effects on intracellular calcium levels. PKGIα can phosphorylate calcium-activated potassium channels and cause membrane hyperpolarization via channel opening and potassium escape [45, 46]. The hyperpolarized membranes then inhibit surrounding voltage-gated calcium channels [47]. In addition, PKGI is able, via phosphorylation, to inhibit the same channels and to prevent intracellular calcium entry [48]. Activation of the plasma membrane calcium/ATPase pump and of the sarcoplasmic reticulum calcium/ATPase pump is an additional mechanism by which PKGI lowers intracellular calcium content and inhibits the contractile machinery [49, 50].

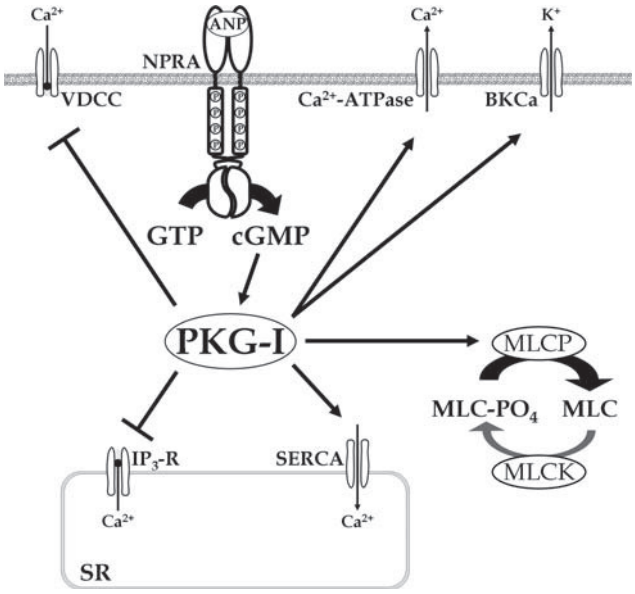

Fig. 2 ANP-dependent VSMC relaxation. ANP is able to relax VSMC through PKGI activation. The kinase phosphorylates several targets that are linked to cytoplasmic calcium content. Calcium is sequestered by the phosphorylation of plasma membrane calcium-ATPase (Ca^{2+}-ATPase), and the sarcoplasmic reticulum calcium-ATPase (SERCA) pump lowers cytoplasmic calcium concentration. Blockade of the IP_3 receptor and the voltage-dependent calcium channel (VDCC) prevents calcium entry. Phosphorylation of the calcium-activated potassium channel (BKCa) causes membrane hyperpolarization through increased potassium efflux. Activation of myosin light chain phosphatase (MLCP) by PKGI releases contraction and lowers calcium sensitivity. *MLC*—myosin light chain, *MLCK*—myosin light chain kinase

The kinase also affects calcium release from the sarcoplasmic reticulum by phosphorylating the IP_3 receptor and its IP_3 receptor-associated PKGI substrate [51, 52]. Direct effects on contractile mechanisms come from PKGI-dependent phosphorylation and activation of myosin light chain phosphatase which decrease global myosin light chain phosphate content [38, 53, 54]. Altogether, these actions, illustrated in Fig. 2, contribute to smooth muscle cell relaxation.

The kidney and renin–angiotensin–aldosterone-system antagonism

The kidney is one of the best-known targets of ANP, with rising cGMP concentration increasing the glomerular filtration rate (GFR) through coordinated efferent arteriolar vasoconstriction and afferent arteriolar vasodilatation [55]. These events are exclusively mediated by NPRA present in glomeruli as they can be antagonized by HS-142 and A71915 [56–58]. Angiotensin II-dependent reabsorption of sodium and water by proximal tubules is inhibited by peritubular ANP stimulation [59]. cGMP also suppresses sodium transport from the collecting ducts by inhibiting amiloride-sensitive cation channels [60]. Juxtaglomerular cells are also affected as they stop secreting renin after intrarenal ANP injection through a PKGII-dependent mechanism [61, 62]. In addition to this effect, the renin–angiotensin–aldosterone system (RAAS) is antagonized directly at the level of the adrenal glands by ANP. The peptide reduces angiotensin II-stimulated, ACTH-induced, and basal aldosterone levels [63–65]. The pathways responsible for the inhibition of aldosterone secretion remain unclear, but a sound hypothesis has been proposed. ANP, through cGMP, could activate cyclic GMP-stimulated PDE2 which degrades cAMP in the aldosterone synthesis signaling pathway [66]. It could also involve the synthesis and phosphorylation of regulatory protein(s), disturbing the entire steroidogenesis pathway [67, 68]. Altogether, these actions help maintain volume homeostasis by increasing fluid and electrolyte excretion.

cGMP and cell proliferation

Although cGMP involvement in cell proliferation is still controversial, NPs are clearly anti-proliferative agents negatively regulating vascular growth. Controversy arose when studies demonstrated the angiogenesis potential of NO donors in several cell lines. Indeed, these compounds were able to increase vascular endothelial growth factor (VEGF) mRNA levels in a cGMP-dependent manner and promote vessel formation through the cGMP pathway [69–72]. However, ANP is a strong inhibitor of cell proliferation for many cell lines including renal mesangial cells, VSMC, endothelial cells, and cardiac fibroblasts [73–76]. These anti-proliferative effects are mediated by NPRA through a cGMP-dependent mechanism which inhibits the RAAS and mitogen-activated protein kinase pathways [77, 78]. CNP is known to be a strong inhibitor of VSMC proliferation, 10 times stronger than ANP, and may be implicated in vascular remodeling [79]. The peptide has been shown to inhibit thickening of the carotid artery intima after balloon catheter injury [80–82]. The autocrine action of CNP on cardiac fibroblasts may also prevent cell proliferation, thus protecting the heart from fibrosis. This has been hypothesized in view of the fact that the CNP-dependent elevation of cGMP inhibits DNA synthesis and collagen production in cultured cardiac fibroblasts [83]. NPRA may also play a role in cancer progression. Indeed, a recent study showed that NPRA-deficient mice are protected from lung, skin, and ovarian cancer [84] via a complex mechanism implicating its effects on inflammation and autoregulation of the receptor expression. Moreover, NPRA deficiency down-regulates VEGF expression while up-regulating the expression of tumour suppressor retinoblastoma protein and implicating NPRA in tumour angiogenesis [84].

Pro- and anti-apoptotic effects

Apoptosis, which is a well-organized cell death, is an essential process for normal development and many pathophysiological conditions. Post-GC signaling, through cGMP, is involved in the regulation of several apoptosis-associated genes which can have either pro-apoptotic or anti-apoptotic effects. Indeed, cGMP elevation can induce apoptosis in VSMC, cardiomyocytes, and endothelial cells [85–88]. The pro-apoptotic effects of cGMP are mediated by PKGI [85, 88]. The kinase may indirectly increase apoptosis through JNK activation and phosphorylation/degradation of ß-catenin which normally drives the expression of several anti-apoptotic genes [89–91]. In addition, in cardiomyocytes, ANP-induced elevation of cGMP concentration inhibits the expression of Mcl-1 mRNA, an anti-apoptotic Bcl-2 homolog, and promotes apoptosis [86]. In some cell lines, cGMP can also have an anti-apoptotic counterpart. In cerebellar neurons, the protective effects of cGMP are correlated with increased CREB phosphorylation and Bcl-2 expression [92]. Down-regulation of the pro-apoptotic Bcl-2 binding protein BNIP3 by cGMP also protects hepatocytes from apoptosis [93]. Since data have proven that cGMP can be both pro- and anti-apoptotic, differences in their mechanisms clearly appear to be cell specific.

Fat cell function and metabolism

The fairly recent association between GC signaling and fat metabolism has rapidly gained interest due to the large number of obesity-related diseases. This sudden interest is mainly due to the fact that ANP-mediated lipolysis is specific to primates, and rodent adipocytes are inefficient in these studies since they possess a low NPRA/NPRC ratio which promotes NP clearance [94]. Lipolysis is induced by both ANP and BNP, but not by CNP, and relies on the cGMP-dependent pathway as it can be mimicked by a cGMP analog [95]. PKGI activation by cGMP induces perilipin and hormone-sensitive lipase (HSL) phosphorylation which are the initiation steps of lipolysis [95]. In addition to cGMP-dependent lipolysis, catecholamines are also able to stimulate lipolysis through cAMP elevation and protein kinase A (PKA) activation [96]. Both the pathways, cAMP and cGMP, converge to the same goal, which is the stimulation of lipolysis. However, insulin-dependent activation of PDE3B, the cAMP-hydrolyzing PDE, inhibits lipolytic mechanisms initiated by the β-adrenoreceptor [97]. This cross-talk between the lipogenesis effect of insulin and the lipolytic action of NPs does not exist in human fat cells as PDE5A activity is not regulated by insulin [97]. In addition to lipolysis, ANP is able to inhibit visceral adipocyte growth by a cGMP-dependent mechanism [98]. On the contrary, NP-induced lipolysis can be counteracted by the RAAS. Adipocytes have all the machinery required for angiotensin II signaling, and the peptide has been shown to stimulate lipogenesis and preadipocyte differentiation [99, 100]. Indeed, stimulation of adipocytes with angiotensin II through the type 2 angiotensin receptor causes the transcriptional up-regulation of fatty acid synthase (FAS) gene [99]. FAS is one of the first enzymes in the lipogenic pathway, and it converts malonyl-CoA into stearic acid-CoA; the following steps leading to triacylglyceride formation are made up of several enzymes located on the endoplasmic reticulum membrane [101]. The ability of angiotensin II to inhibit NP-dependent lipolysis relies on phospholipase C (PLC) activation and implies two separate processes. Phosphatidylinositol bisphosphate is digested into DAG and IP_3 under the action of PLC [102]. DAG and IP_3, respectively, activates PKC and increases cytoplasmic calcium content [102]. Calcium elevations activate PDE3B, which will hydrolyze the second messenger cGMP into GMP, thus affecting PKG activation sensitivity [103]. In addition, angiotensin II has been shown to directly inhibit the transcription of murine NPRA gene [104]. In this context, angiotensin II and ANP counterbalancing effects may have important roles in visceral adipose tissue development [98]. These processes are briefly summarized in Fig. 3. ANP has also been postulated to be a potential regulator of fat gain and BP increase in a postmenopausal mouse model through the reduction of ANP levels [105]. Estradiol treatment improves ANP levels in these mice by both lowering NPRC content and augmenting ANP synthesis, which suggest possible cross-talk between estrogens and the NP system in adipose tissue dynamics [105].

Pathophysiological role in hypertension and metabolic syndrome: experimental genetics and signaling disorder

Role in metabolic syndrome progression

Obesity together with hypertension are the leading risk factors for the development of cardiovascular diseases, and the NP system is able to maintain the tight regulation set between proper body weight and an unhealthy overweight condition. However, this fragile equilibrium can easily be destroyed by anything which can affect NPs or their receptor levels. The anti-obesity power of NPs relies on several lines of metabolic evidence which all converge to triglyceride lipolysis and β-oxidation. Earlier, we mentioned that ANP promotes lipid mobilization through HSL activation, but this lipolysis is enhanced when endurance exercises are performed [106]. Increases of non-esterified fatty acids (NEFA) by HSL activation will then fuel

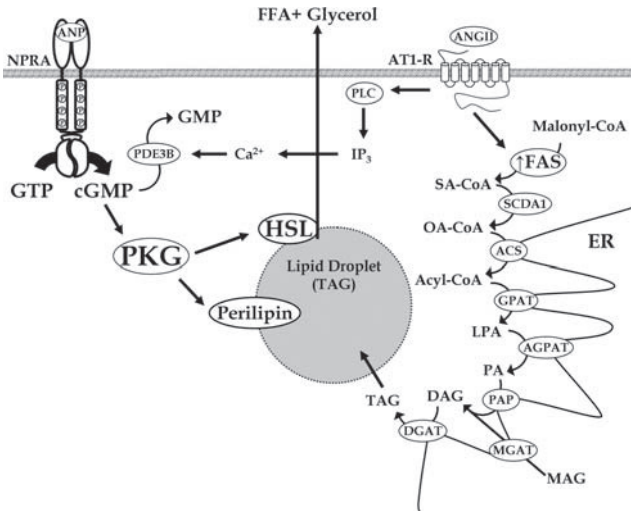

Fig. 3 Antagonistic effects of ANP and angiotensin II stimulation in human adipocytes. NPRA stimulation triggers lipolysis through cGMP production and protein kinase G (PKG) activation. Subsequent phosphorylation of hormone-sensitive lipase (HSL) and perilipin by PKG breaks up triacylglycerol into free fatty acids (FFA) and glycerol. However, this pathway can be inhibited by angiotensin II stimulation through calcium elevation, and, thus, Ca^{2+} activates phosphodiesterase-3B (PDE3B) which hydrolyzes cGMP to release GMP. The antagonistic effects of angiotensin II also derive from its ability to produce triacylglycerol (TAG). Angiotensin II stimulation induces the transcription of fatty acid synthase (FAS), the starting enzyme of the lipogenesis pathway. Lipogenesis pathway: *SA-CoA*—stearic acid-CoA, *SCDA1*—stearoyl-CoA desaturase-1, *OA-CoA*—oleic acid-CoA, *ACS*—acyl-CoA synthase, *GPAT*—glycerol-3-phosphate acyltransferase, *LPA*—lysophosphatidic acid, *AGPAT*—acylglycerol-3-phosphate acyltransferase, *PA*—phosphatidic acid, *PAP*—phosphatidic-acid phosphohydrolase, *DAG*—diacylglycerol, *MGAT*—monoacylglycerol acyltransferase, *MAG*—monoacylglycerol, and *DGAT*—diacylglycerol acyltransferase

working muscles during endurance training as they cannot rely on glucose storage for a long period of time. Recent studies have demonstrated a strong link between the ANP/NPRA system and postprandial state. Indeed, both genes are positively associated with lowered BP, elevated venous glycerol and NEFA levels, increased lipid oxidation rates and enhanced adipose tissue blood flow [107, 108]. Moreover, cGMP has been shown to trigger mitochondrial biogenesis through the induction of peroxisome proliferator-activated receptor-γ coactivator-1α [109]. Together, these effects promote adipose tissue turnover by NEFA release, an efficient utilization of this energy source by enhanced β-oxidation due to multiplying mitochondria and globally-improved cardiac and skeletal muscle metabolism. This is, however, an ideal scenario which is different in overweight subjects. Indeed, obese individuals tend to have lower NP levels than the so-called lean "normal" subjects, whereas metabolic syndrome (MetS) patients also have lower ANP and BNP levels [110–112]. These levels can be explained by downregulated cardiac secretion of NPs because the N-terminal portion of cleaved pro-ANP and pro-BNP, unable to bind any NPR, is present at lower levels in obese subjects [112]. Obesity also influences receptor number in adipocytes, affecting the ratio of expressed NPRA/NPRC. Indeed, in obese, hypertensive patients, the NPRA/NPRC ratio is reduced in subcutaneous adipose tissue, suggesting abnormal clearance activity versus NPRA activation which will greatly reduce NP efficiency [113]. The combined effects of decreased NP secretion added to increased clearance could have a significant impact on lipid storage, especially when caloric intake is excessive. However, this condition is not permanent and can be reversed by fasting which dramatically downregulates NPRC expression in adipose tissues [114]. In obese, hypertensive patients, ANP infusion after hypocaloric dieting exerts more pronounced effects in terms of BP diminution, natriuresis, diuresis, and cGMP elevation than it does before low caloric intake, indicating enhanced NPRA activation after caloric restriction [115]. Another component of MetS which has been linked to NP levels is insulin resistance. In Framingham study participants, an inverse association was found between NP and both plasma glucose and insulin levels, suggesting that lower circulating NP levels could be an additional manifestation of MetS [116]. It has also been reported that ANP can directly inhibit glucagon secretion from pancreatic islets [117]. In a low NP condition, these two separate mechanisms contribute to impaired glycaemia levels, promote insulin resistance, and inevitably lead to type 2 diabetes development.

Role of the NP system in BP regulation and diagnostic and therapeutic potential in hypertension

Hypertension alone or associated with MetS is a complex multifactorial disease controlled, in part, by the NP system. The contribution of NPs or their receptors has been studied in different rat and mouse models. The combined effects of NPs on volume regulation (diuresis/natriuresis) and vasorelaxation control overall BP. An eightfold increase in plasma ANP levels is able to decrease BP by 30 mmHg without inducing urinary volume or salt excretion in transgenic mice [118]. Double ANP gene knockout mice have 8–23 mmHg higher BP on a standard diet with 0.5% NaCl or a 2% NaCl diet [119]. The heterozygous strain has normal BP on a normal diet, but a high-salt diet can propel it 27 mmHg higher than in the controls, indicating that reduced ANP levels can lead to salt-sensitive hypertension [119]. Homozygous ANP knockout mice exhibit left and right ventricular hypertrophy which is accompanied by increased expression of extracellular matrix proteins and metalloproteinases that are probably normally repressed by ANP [120]. Renal function is also disrupted in these mice

as they cannot excrete sodium after saline infusion, even if the GFR is similar between ANP-null and control mice [121]. This is caused by high sodium and chloride reabsorption by the collecting ducts, suggesting that ANP is essential for natriuresis in acute intravascular volume expansion [121]. Manipulation of NPRA produces direct and proportional correlation between BP and the number of gene copies present [122]. Thus, homozygous deletion of NPRA elicits salt-resistant hypertension and an increased incidence of sudden death and cardiac hypertrophy caused by overactive Na+/H+ exchanger 1 (NHE-1) [123–125]. Selective deletion of NPRA in the heart results in mild hypertrophy, heightened ANP secretion, and reduced BP probably due to the systemic action of ANP [126]. NPRA deletion in smooth muscle cells has no effect on BP under basal conditions, but mice lose their ability to vasorelax under ANP infusion, and this leads to rapid BP elevation after acute volume expansion [127]. NPRA deletion in selective vascular endothelial cells evokes significant hypertension, cardiac hypertrophy, and prevention of ANP-dependent fluid extravasation into the interstitial compartment [128]. On the contrary, NPRA overexpression decreases BP and protects against salt-sensitive hypertension, while cardiac-specific overexpression of NPRA in NPRA-deficient mice reduces myocyte size and ANP expression [122, 129]. BNP overexpression in transgenic mice culminates in a significant rise of plasma cGMP levels and lowers BP in comparison to wild-type animals [130]. Elevated BNP in circulation also causes skeletal abnormalities through a high turnover of endochrondral ossification and increased height of the cartilaginous primordium [131]. BNP deletion does not produce hypertension or ventricular hypertrophy but results in multifocal fibrotic lesions in ventricles which grow in size and number in response to ventricular pressure overload [132]. Deletion of CNP gene leads to somatic dwarfism, and its overexpression rescues the phenotype in CNP-null mice but does not affect BP [133, 134]. Similarly, NPRB gene-deleted mice are not hypertensive but show dysfunctional endochondral ossification and diminished longitudinal growth of limbs and vertebra [135]. In transgenic rats, overexpression of a dominant negative version of NPRB causes BP-independent cardiac hypertrophy and heightened heart rate, suggesting a role for NPRB signaling in cardiac growth [136]. Deletion of NPRC culminates in slightly lower BP, mild diuresis, decreased blood volume, and increased bone growth, phenotypes that are all linked to impaired clearance of NPs [137]. The locus on rat chr 2 containing GC-A has been shown to cosegregate positively with BP in six different rat crosses with genetically distant hypertensive and normotensive progenitors. Data from congenic strains have confirmed the existence of a BP quantitative trait loci (QTL) at the GC-A locus [138].

In humans, our group performed a whole genome scan initially with microsatellite markers and then with a high density of single nucleotide polymorphism markers (SNPs) in a family cohort with hypertension and dyslipidemia. We identified significant QTL for blood pressure and other hypertension-related traits. We found a QTL with significant logarithm of odds (LOD) score for hypertension and obesity-associated hypertension (LOD score $\geq$1.9) at position 1p36 where ANP and BNP genes are located [139]. We also found a chromosomal region at position 1q which was significantly associated with several metabolic phenotypes such as BMI, percentage of body fat, insulin levels in addition to BP etc.[140]. A total of 13 phenotypes mapped between positions 170–233 centiMorgan (cM) with LOD scores ranging between 2.1 and 3.9 [140]. The region spanning 63 cM contains several candidate genes including the NPRA gene. A recent study also showed a strong link between three SNPs and the NP circulating levels. Indeed, the presence of the minor allele of the three SNPs, rs5068, rs198358, and rs632793 within the ANP and BNP genes were directly related to increased concentrations of these NPs in both normotensive and hypertensive patients [141]. Moreover, the minor alleles of rs5098 and rs198358 were also found to be associated with slightly lower systolic and diastolic pressures and reduced risk of developing hypertension [141]. These human genetic studies demonstrated that variations in NP genes can modify the peptide's circulating levels and that ANP/BNP and NPRA genes can be included in a set of positional candidate genes for blood pressure and obesity disorders. More studies are needed as we begin to understand the complexity of gene–gene interaction within the human chromosome 1.

Natriuretic peptides are now useful diagnostic tools for many pathological conditions. Thus, elevation of circulating ANP and BNP levels is strongly associated with congestive heart failure, hypertension and chronic renal failure [142–144]. Plasma BNP level is a marker of left ventricular function, a predictor of post-stroke mortality, post-cardiac surgery atrial fibrillation, and can also serve to assess the prognosis in patients with congestive heart failure [144–147]. As we mentioned earlier, low levels of NPs are often associated with the pathophysiological condition of MetS and hypertension. Thus, many studies have been conducted to clinically restore normal levels of NPs to manage these conditions. Acute ANP injection, tested in hypertensive patients, decreases BP with increased natriuresis and diuresis [148, 149]. Chronic ANP infusion in hypertensive monkeys also leads to a persistent decrease of BP [150]. Even if this approach is positive, long-term treatment of hypertension with these peptides is clearly impossible due to practical aspects of the technique. Gene therapies have also been tested for more long-term control

of hypertension. Indeed, intravenous injection of a human ANP DNA construct results in a constant 21-mmHg reduction of BP in young SHRs without any apparent side-effects [151]. However, gene therapies are controversial, and the more classical and accepted methods of manipulating hormone levels are based on a pharmacological approach. Thus, infusion of anaritide, a synthetic version of ANP, decreases BP and increases natriuresis and diuresis in patients with hypertension or heart failure [152–155]. Nesiritide, the recombinant form of human BNP, has been shown to induce vasorelaxation, lower aldosterone levels, and promote salt and water excretion in patients with heart failure [156–158]. However, nesiritide was recently found to be associated with an elevated risk of renal dysfunction and mortality [159, 160]. Other means include the control of NP degradation by inhibition of neutral endopeptidases (NEP). Thus, blocking NEP causes an elevation of circulating NP and a greater hypotensive effect, especially when combined with angiotensin-converting enzyme inhibition [161–163]. However, the inhibitor omapatrilat has been shown to heighten the risk of angioedema by threefold, especially in black individuals [163]. Further investigations are needed to enhance the efficacy and safety of treatments derived from NP system manipulations.

Conclusion

The NP system was a milestone discovery that confirmed the endocrine role of the heart for the first time in the early 1980s. From its vasodilatory, natriuretic, and diuretic actions, knowledge about this system has evolved to a degree of complexity unsuspected at that time. Now, through cGMP generation, NPs are involved in several other mechanisms, such as cell proliferation, apoptosis, RAAS inhibition, and fat cell function. The latter point is of growing interest in lipid metabolism and has become an important issue in the fight against obesity. This pandemic condition is one of the risk factors leading to hypertension development and MetS progression. Thus, understanding, at least in part, the lipid mobilization pathways controlled by NPs could have a positive impact in MetS management. As with hypertension, identifying defects in signaling pathways will certainly help identify mechanisms implicated in lost sensitivity of the NP system. Further studies are needed to investigate problems, such as impaired NPR ratio, lowered NPRA/B content, increased NP clearance levels, and even NEP dynamics. Through pharmacogenetic studies and personalized medicine targeting the NP system, we will be able to optimize treatment to every patient. We hope that they will advance the development of activators or inhibitors of the NP system for the clinical benefit of patients suffering from hypertension and/or MetS.

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