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Review

Natriuretic peptides and cardio-renal disease

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ABSTRACT

The natriuretic peptide (NP) system is an important endocrine, autocrine and paracrine system, consisting of a family of peptides which provide cardiac, renal and vascular effects that, through their beneficial physiological actions, play a key role in maintaining overall cardiovascular health. Traditionally, the pathophysiological origins of cardio-renal disease have been viewed as the domain of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS), with inappropriate activation of both systems leading to deleterious changes in cardio-renal function and structure. Therapies designed to suppress the RAAS and the SNS have been routinely employed to address the consequences of cardio-renal disease. However, it is now becoming increasingly apparent that enhancing the beneficial physiological effects of the NP system may represent an attractive alternative therapeutic approach to counter the pathophysiological effects of disease. In particular, innovative therapeutic strategies aimed at enhancing the physiological benefits afforded by NPs while simultaneously suppressing the RAAS are generating increasing interest as potential treatment options for the management of cardio-renal disease.

1. Introduction

Cardio-renal diseases such as hypertension, heart failure (HF), and chronic kidney disease (CKD) are highly prevalent and associated with significant morbidity and mortality, with the human and economic burden of these diseases only expected to worsen as populations progressively age. Existing therapies to combat cardio-renal disease have traditionally targeted the renin–angiotensin–aldosterone system (RAAS) and to a lesser extent the sympathetic nervous system (SNS) [1–4]. However, despite the proven benefits of these therapies, there is still a considerable unmet need in the effective management of cardio-renal disease and it is clear that new therapeutic options are required to improve patient care.

The natriuretic peptides (NPs) are a family of cardiac- and vascular-derived hormones which, via multiple effects on vascular tone, intravascular volume and redistribution, neurohormonal activity, cardiovascular (CV) remodeling and energy metabolism, play an important role in the maintenance of CV homeostasis [5–9]. As such, enhancing the beneficial physiological effects mediated by NPs is seen as a potential therapeutic approach for the treatment of cardio-renal disease.

This paper will review the physiology of the NP system and briefly consider its interactions with the RAAS and the SNS in the neurohormonal control of cardio-renal function. It will discuss how the origin of the pathophysiology of cardio-renal disease, specifically hypertension, HF and CKD, may extend beyond inappropriate activation of the RAAS and SNS to include disruption of the NP system. It will also consider how novel therapeutic agents that enhance NP levels, in particular those that simultaneously suppress the RAAS, may open up a new horizon in the management of cardio-renal disease.

2. The natriuretic peptide system

2.1. Natriuretic peptides

The NP system is an important endocrine, autocrine and paracrine system, which acts to maintain CV homeostasis [9]. It consists primarily of three genetically distinct, but structurally related peptides: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) [10,11] (Table 1). ANP is predominantly synthesized in the atria and released in response to atrial distension [12,13]. BNP is mainly produced and secreted by ventricular myocytes following volume overload, leading to ventricular wall stretch [12,14,15]. In contrast to ANP, the circulating physiological levels of BNP are generally very low and only become more notable in pathological disease states [16]. This raises the intriguing possibility that ANP may represent the 'physiological' hormone of the NP system, influencing and controlling normal cardio-renal activities whereas, in contrast, BNP might function more as a 'cardiac stress response' hormone, only coming to prominence when compensatory responses are required to address pathological challenges [17]. CNP is mainly secreted by the vascular

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Table 1
Overview of the three principal members of the NP system: ANP, BNP and CNP.

Natriuretic peptide	ANP	BNP	CNP
Structure	28 amino acid peptide	32 amino acid peptide	22 amino acid peptide
Main site of synthesis	Atria	Ventricles	Vascular endothelial cells
Main secretory trigger(s)	Atrial distension	Volume overload (leading to ventricular wall stretch)	Cytokines e.g. IL-1, TNF, endothelium-dependent agonists e.g. acetylcholine
Proposed main role	Physiological hormone	Cardiac stress response hormone	?
Receptor	NPR-A	NPR-A	NPR-B
Receptor coupling mechanism/ second messenger	↑Guanylate cyclase/cGMP	↑Guanylate cyclase/cGMP	↑Guanylate cyclase/cGMP
Main physiological effects of NP	Natriuresis and diuresis Vasodilation RAAS and SNS suppression ↑Renal blood flow and GFR ↑Myocardial relaxation Lipid mobilization, metabolic effects Antihypertrophic and Antifibrotic ↑Endothelial permeability Anti-inflammatory	Natriuresis and diuresis Vasodilation RAAS and SNS suppression ↑Renal blood flow and GFR ↑Myocardial relaxation Lipid mobilization, metabolic effects Antifibrotic	Vasodilation Antihypertrophic and antifibrotic Anti-inflammatory Antithrombotic Bone growth regulation
Clearance of NP/enzymatic degradation	Clearance via NPR-C NEP degradation	Clearance via NPR-C NEP degradation	Clearance via NPR-C NEP degradation

cGMP = cyclic guanosine monophosphate; GFR = glomerular filtration rate; IL-1 = interleukin-1; NEP = neprilysin; NP = natriuretic peptide; NPR = natriuretic peptide receptor; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system; TNF = tumor necrosis factor.

endothelium following stimulation by pro-inflammatory cytokines (e.g. interleukin-1 and tumor necrosis factor) and endothelium-dependent agonists (e.g. acetylcholine) [7,14,18,19]. Like BNP, circulating levels of CNP are also low in the absence of disease [8].

2.2. Natriuretic peptide receptors

NPs interact with three different types of NP receptor: A (NPR-A), B (NPR-B) and C (NPR-C). The NPR-A binds both ANP and BNP, whereas NPR-B binds CNP [11,20]. Binding of NPs to either NPR-A or NPR-B activates membrane-bound particulate guanylate cyclase and leads to the stimulation of the intracellular cyclic guanosine monophosphate (cGMP)-dependent second messenger signaling cascade, which mediates the majority of the physiological actions of NPs [11,20,21]. Such actions help to control BP and intravascular volume, modulate vascular tone, regulate cardiac and vascular remodeling, and influence energy metabolism [5–9]. NPR-C is primarily viewed as a clearance receptor that binds and internalizes NPs to remove them from the circulation [22]. However, increasing evidence suggests that NPR-C may also fulfill a variety of biological functions, potentially mediated via inhibition of adenylate cyclase and activation of phospholipase C [22–24]. Although the exact physiological role of the NPR-C is still to be confirmed, most of its potential biological activity is thought to stem primarily from NPR-C binding of CNP (in preference to ANP or BNP) [23].

2.3. Physiological effects of natriuretic peptides

2.3.1. Blood pressure and intravascular volume

NPs play a pivotal role in the maintenance of BP and intravascular volume. BP control may be achieved through the regulation of vascular tone, caused by a direct relaxant effect of NPs on vascular smooth muscle cells [21]. Furthermore, the NPs help to regulate BP by suppressing the RAAS, reducing sympathetic tone and inhibiting secretion of the vasoconstrictor, endothelin-1 (ET-1) [6,11,21]. In addition, NPs are also fundamental to the regulation of intravascular volume, influencing electrolyte and fluid balance in the kidneys, and mediating direct effects on endothelial permeability in the vasculature [25,26]. In the kidneys, the inhibition of sodium reabsorption in the proximal and distal nephron by NPs leads to the promotion of natriuresis and diuresis, driving decreases in intravascular volume and BP [11,21]. These effects of NPs on electrolyte/fluid balance are thought to be mediated more by ANP and BNP than CNP [8]. ANP and BNP increase renal blood flow and glomerular filtration rate (GFR), further optimizing renal function [6,20,21]. In the vasculature, ANP causes an increase in endothelial permeability that contributes towards hypovolemia, promoting redistribution of plasma proteins and fluid from the intravascular space to the interstitial space [16,25].

2.3.2. Cardiac and vascular remodeling

While the positive influence of NPs on BP and intravascular volume is representative of classic endocrine activity, complementary autocrine and paracrine actions of NPs are also thought to contribute towards promotion of general cardio-renal health [7,9,27].

Cardiac and vascular remodeling is implicated in the pathogenesis of cardio-renal disease, including hypertension, HF and CKD [28–30]. Increasing evidence suggests that NPs play a significant role in attenuating or inhibiting the processes that contribute to remodeling, including hypertrophy, fibrosis and inflammation [27]. For example, preclinical data have demonstrated the ability of ANP to inhibit cardiomyocyte hypertrophy induced by either angiotensin II (Ang II) or ET-1, both vasoactive peptides with deleterious effects on the cardio-renal system, as a result of cGMP-dependent processes [31]. Recent data suggest that ANP may protect against Ang II-induced cardiac remodeling by minimizing events that are key to the inflammatory process including macrophage infiltration and expression of pro-inflammatory factors [32]. Meanwhile, in vitro evidence indicates that ANP can attenuate norepinephrine-induced growth of cardiac myocytes and fibroblasts due to a cGMP-mediated inhibition of norepinephrine-induced influx of Ca^{2+} [33]. These findings may highlight a key role of the NP system in countering the adverse effects of increased SNS activity on the myocardium. In addition, antifibrotic effects of ANP have been reported in cardiac fibroblasts, inhibiting cell proliferation and collagen synthesis induced by transforming growth factor-β (TGF-β), a key mediator of cardiac fibrosis, through cGMP-dependent pathways [34].

However, evidence to support the beneficial effects of NPs in countering CV remodeling is not restricted to ANP. In vitro data also support the antifibrotic effects of BNP, with TGF-β-induced fibrosis inhibited by BNP in cardiac fibroblasts [35]. Furthermore, in vivo data have demonstrated that CNP attenuates cardiomyocyte hypertrophy and inhibits myocardial interstitial fibrosis induced by Ang II [36]. The high concentration of CNP in the endothelium is believed to facilitate an important protective role within the vasculature, inhibiting pro-inflammatory responses within the vascular wall (including inflammatory cell recruitment and smooth muscle cell proliferation) and promoting angiogenesis [8]. Promotion of angiogenesis by NPs may prove to be particularly beneficial in addressing the consequences of tissue ischemia [37]. In

addition, experimental evidence has demonstrated that CNP can prevent cardiac remodeling after myocardial infarction, further emphasizing the CV protective actions of NPs [38].

2.3.3. Energy metabolism

An additional important role of NPs in regulating energy homeostasis is also emerging [5,39]. NPs are thought to interact with a number of tissues and organs, including white and brown adipose tissues, skeletal muscle, the liver and the pancreas, to control lipid and carbohydrate metabolism [5]. ANP and BNP, via stimulation of NPR-A and the subsequent activation of intracellular cGMP, promote lipolysis and the mobilization of free fatty acids in human adipocytes [5,40]. Both ANP and BNP also enhance expression and secretion of adiponectin, an adipokine with insulin-sensitizing properties, in primary cultures of human adipocytes [41], with ANP shown to increase adiponectin concentrations from baseline in healthy subjects and in patients with congestive HF [41,42]. In addition, the ANP/cGMP signaling pathway increases β-cell mass and insulin secretion in the pancreas [5]. Findings from a genetic variant study have suggested that increased availability of ANP may confer cardiometabolic protection, although further studies are required to confirm these data [43]. Furthermore, it has been proposed that chronic upregulation of NPR-C may contribute towards obesity and obesity-related CV and metabolic disorders such as type 2 diabetes and metabolic syndrome [5,39].

2.4. Enzymatic degradation of natriuretic peptides

In addition to clearance by NPR-C, NPs are removed from the circulation through enzymatic degradation by neprilysin (NEP), a membrane-bound enzyme expressed mostly in the kidneys [44,45]. ANP and CNP are the NPs most susceptible to degradation by NEP, whereas the enzyme has a lower affinity for BNP [46]. NEP also degrades other vasoactive peptides including vasodilators, e.g. substance P and bradykinin, and vasoconstrictors such as ET-1 and Ang II [47–51]. Consequently, the net physiological effect of NEP will depend on the balance between its actions on vasodilators versus vasoconstrictors.

Overall, when the wide range of beneficial physiological effects of NPs is considered, it is evident that the NP system is a vital contributor to the maintenance of CV homeostasis. Arguably the positive influence of the NP system on key organs and tissues throughout the body should be capitalized on to promote CV health and when necessary, negate the effects of disease. Indeed, the NP system might be regarded as the body's own natural defense mechanism, helping to counter the detrimental effects that stem from inappropriate over-activation of the RAAS and SNS. However, it is reasonable to think that, at least in human disease, even a maximal activation of the NP system may not be able to counteract or prevail over the hyperactivation of 'emergency' mechanisms such as the RAAS and the SNS, which are apparently prevalent in the human species. At first glance, NEP appears to represent a logical target for therapeutic intervention — inhibiting NEP would lead to enhanced levels of NPs and the potential for a greater physiological influence of NPs throughout the body. However, there are multiple substrates for NEP, some of which have opposing biological actions to NPs such as Ang II. Therefore, later in this review we will address how NEP inhibition can only be considered a viable therapeutic approach when in the context of simultaneous suppression of the RAAS.

3. The role of the natriuretic peptide system in the neurohormonal control of cardio-renal function

Neurohormonal systems such as the RAAS and the SNS play an important role in modulating key parameters of CV homeostasis including vascular tone, electrolyte and fluid regulation, and CV remodeling [52–57]. The NP system, together with the RAAS and SNS, is now recognized as a key neurohormonal system and considerable interaction is thought to take place between these three systems to maintain efficient cardio-renal homeostatic control [7,45,53,58]. In general, the beneficial physiological actions of the NP system are counter-regulatory to those of the other two systems, in particular the RAAS (Fig. 1). Indeed, the NP system may be considered as a 'natural antagonist' of the RAAS and the SNS. The NP system decreases renin and aldosterone secretion, resulting in suppression of the RAAS [59,60]. In addition, NPs interfere with autonomic and baroreflex control of the circulation, leading to an inhibition of SNS effects and an increase in parasympathetic nerve activity [61–63]. The RAAS and the SNS operate in a mutually cooperative manner [64]. Ang II, the principal effector hormone of the RAAS, binds with angiotensin type 1 (AT_1) receptors to increase activation of the SNS [65]. While sympathetic drive increases renin secretion from the kidneys [66], thereby enhancing RAAS activity, data show that endogenous activation of the SNS can reduce secretion of ANP [67]. What remains to be determined is the extent to which the physiological benefits mediated by NPs relate to their direct biological actions on end organs and tissues versus any indirect effects from antagonizing the detrimental actions of the RAAS and SNS.

4. Pathophysiology of cardio-renal disease

To date, the pathophysiology of cardio-renal disease has traditionally been viewed as a consequence of inappropriate over-activation of the RAAS and the SNS. Yet with increasing awareness of the multiple physiological benefits of NPs, we should now consider how disruption of the NP system may also lead to the development of disease. Therefore, cardio-renal disease pathophysiology may be addressed not only by targeting an inappropriately activated RAAS or SNS, but also by simultaneously enhancing the CV and renal health-promoting benefits of the NP system.

First we provide a brief reminder below of why the deleterious effects of the RAAS and the SNS are regarded as fundamental to the development and progression of cardio-renal disease. We then consider how attenuating the physiological benefits of the NP system may prove detrimental to CV and renal health.

4.1. Renin–angiotensin–aldosterone system

The role of the RAAS in the regulation of the CV system, mediating physiological effects including vasoconstriction, and sodium and water retention to control BP and electrolyte/fluid balance, is well established [45,53]. However, when activated inappropriately, it is widely recognized that the RAAS becomes a significant contributor to the pathophysiology of cardio-renal disease [68–70], due in part to mediating cardiac and vascular hypertrophy, renal fibrosis, pro-inflammatory processes and oxidative stress [45,71]. As the subject of intensive interest and research across several decades, the RAAS has taken on an increasing level of complexity with the discovery of numerous additional components and pathways [65,71]. However, the actions of Ang II and aldosterone are believed to be fundamental to the majority of the physiological and pathological effects of the system [4,45,71,72], and agents designed to inhibit the RAAS are accepted as key components of the pharmacological armamentarium for the management of hypertension, HF and CKD [1–4].

4.2. Sympathetic nervous system

Although perhaps less well documented than is the case for the RAAS, evidence suggests that increased activation of the SNS is also a key feature in the development of cardio-renal disease [73–75]. In addition to increased vasomotor tone and cardiac output, chronic activation of the SNS causes sodium and water retention, pro-inflammatory processes and cardiac and vascular remodeling [76]. In the early stages of HF, the SNS responds to the ailing heart by restoring cardiac output and increasing peripheral vasoconstriction in an effort to maintain homeostasis [77,78]. This initial response by the SNS, accompanied by

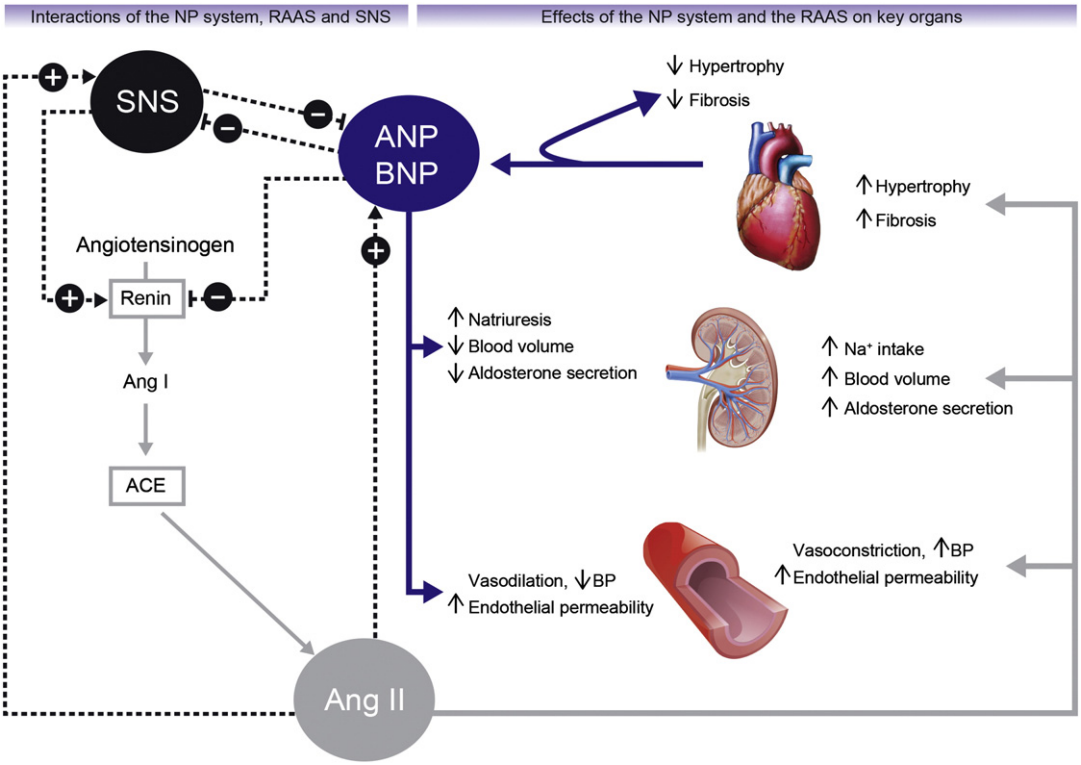

Fig. 1. Schematic diagram to show how the NP system, the RAAS and the SNS interact in order to maintain cardio-renal homeostasis, and how the effects of the NP system and the RAAS on key organs are generally counter-regulatory. ACE = angiotensin converting enzyme; Ang = angiotensin; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; BP = blood pressure; NP = natriuretic peptide; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system.

a similar response by the RAAS, is compensatory (and beneficial). However, prolonged activation of the two systems becomes detrimental and contributes to a worsening picture of HF pathophysiology [77,78]. Chronic activation of the SNS plays a role in the initiation and maintenance of hypertension pathophysiology [79]. Excessive sympathetic activity in hypertension not only drives pathophysiological changes within the heart and the kidneys, but the vasculature is also vulnerable to the deleterious effects of the overactive SNS. By promoting endothelial dysfunction together with vascular smooth muscle cell hypertrophy and proliferation [76], sympathetic overactivity is a key factor in the stiffening of large arteries [80], a possible precursor to the development of hypertension [81].

4.3. Natriuretic peptide system

4.3.1. Hypertension

As discussed earlier, ANP is currently viewed as an important component in the physiological control of cardio-renal function and structure, and its role may be regarded as a physiological factor counteracting, at least partially, the opposing actions of the RAAS and the SNS. Should circumstances develop whereby the positive physiological influence of ANP becomes impaired, then this might be the trigger for the development of cardio-renal disease. Indeed, ANP appears to be a key candidate among potential factors involved in the pathogenesis of hypertension — likely due to the essential role of the kidney and renal function in the development of hypertension, and the effects of ANP on natriuresis, diuresis and hypertension itself [9]. Animal models have demonstrated an exaggerated diuretic and natriuretic response to exogenously administered ANP in spontaneously hypertensive rats compared with normotensive strains [82]. Furthermore, genetically reduced production of ANP has been shown to lead to salt-sensitive hypertension in mice [83]. In humans with mild essential hypertension, increasing arterial plasma levels of synthetic atrial natriuretic factor from two- to three-fold baseline values result in prolonged impact on systolic BP, a shift in fluid from the intravascular to the extravascular space, and a significant increase in salt excretion — with negligible effects on urine volume or GFR, in addition to suppression of the RAAS response of these hypotensive and natriuretic effects [84]. This would suggest that ANP plays an important role in circulatory and renal homeostasis in patients with hypertension.

Preliminary evidence suggests that hypertension might also be the result of a deficiency in biologically active NPs. A lack of activation of biologically active BNP has been reported in patients with grade 1 hypertension versus control subjects [85]. Although the levels of BNP were found to increase with more advanced stages of hypertension, supporting its proposed role as a cardiac stress response hormone, the authors of the study concluded that there may be an impaired response by BNP specifically in the early stages of hypertension [85]. Such a deficiency of biologically active BNP in the initial stages of hypertension may therefore be fundamental to the progression of disease [14,85]. Indeed, recent findings suggest that impaired production and/or increased metabolism of the mature biologically active components of the NP system might contribute to the NP-deficient state in early hypertension [18]. Of interest, the same study also reported that there was no compensatory increase in ANP to counterbalance the apparent deficits of BNP detected in hypertension [18]. Studies with genetic variants of NP genes resulting in higher plasma concentrations of NPs have reported lower BP and a reduced risk of hypertension [86], lending support to what is still an embryonic hypothesis that hypertension may be the result of a deficiency in biologically active NPs.

4.3.2. Heart failure

In chronic HF, early indications were that the NP system was upregulated. Increased levels of BNP and the inactive precursor N-terminal proBNP (NT-proBNP) were linked to worse outcomes and both were regarded as markers of prognosis in chronic HF [87]. This is consistent with other CV disease states, in which elevated levels of BNP have been associated with cardio-embolic stroke [88], myocardial infarction

[89] and atrial fibrillation [90]. Furthermore, in patients with chronic HF with reduced ejection fraction (HFrEF), decreases in NT-proBNP levels were associated with improved CV outcomes [87]. However, perhaps a more complete picture of the dysregulation of the NP system in disease states is now emerging. Using more sensitive mass spectrometry techniques than the previously available diagnostic assays, several studies in patients with HF have reported a lack of mature biologically active BNP and the detection of less active BNP precursors and degradation products [14]. It is proposed that the unexpectedly small physiological responses to the apparently high levels of BNP previously observed in patients with HF may be because most of the BNP detected using conventional diagnostic assays is less biologically active [14]. Consequently, HF may in fact represent a deficient state of biologically active NPs [14]. The increased levels of biologically inert NPs detected by conventional assays may be representative of a stress response of sorts by the NP system to the types of pathological stimuli that would be normally encountered during the early stages of HF, such as cardiac injury or volume overload. However, such a response mounted by the NP system would be inadequate to initiate a physiologically meaningful compensatory reaction to the deteriorating changes in cardio-renal function and structure. The raised levels of biologically inactive BNP detected in chronic HF may therefore signify a potential abnormality in the processing of NPs, leading to a deficit of mature BNP. The observation that expression of myocardial NEP mRNA is increased in patients with HF, leading to an accelerated degradation of NPs, would seem to support the hypothesis that HF may be defined by a deficiency of NPs [91].

4.3.3. Chronic kidney disease

As in patients with HF, plasma levels of NPs are also raised in patients with CKD, again suggesting an upregulation of NPs [92]. Potential mechanisms to explain this increase in NPs include reduced activity of NEP in the kidney, impairment of renal function and the consequences of underlying cardiac pathophysiology [92,93]. In an initial study of patients with primary non-diabetic CKD, plasma concentrations of BNP and NT-proBNP rose in parallel with decreasing renal function and were associated with an increased risk for progression of mild or moderate CKD to end-stage renal disease (ESRD) [94]. After adjusting for factors recognized to be associated with the progression of CKD, NT-proBNP (and not BNP) was found to be an independent predictor of CKD progression, suggesting that it alone may be the more valuable marker of prognosis in patients with CKD [94]. Nevertheless, a more recent study has demonstrated that elevated BNP is suitable as an independent predictor of CKD progression, leading to ESRD [95]. In addition, assessing plasma BNP levels has been shown to be a valuable method to stratify CV risk in patients with CKD, with the highest BNP quartile found to be associated with significantly higher CV risk than the lowest BNP quartile [96]. Our understanding of the full involvement of NPs in renal disease may be further advanced by the utilization of sensitive mass spectrometry assessment techniques. This approach may help determine whether the NPs detected in renal studies to date represent biologically active forms, and whether or not some of the study conclusions have been based on the measurement of less biologically active precursors and degradation products of NPs, as may appear to have been the case in certain HF and hypertension studies.

It is probably a fair assessment that to date, the role of the NP system in health and disease may not have received as much active interest from the scientific research community as has perhaps been the case for the RAAS and the SNS. However, as more evidence of the beneficial physiological effects of the NP system becomes available, and an understanding of the role of NPs in disease states advances, the true value of this family of cardiac and vascular hormones should become increasingly apparent. While it would signify a major shift in mindset for the treating physician, tapping into the potential therapeutic benefits of NPs, with sites of action extending far beyond the vasculature and the kidneys, may prove to be an attractive alternative approach to the use of existing RAAS- and SNS-based therapies in the battle against cardio-renal disease. The potential for NP-based strategies as a therapeutic approach is discussed in the following section.

5. Natriuretic peptide-based therapeutic strategies for the treatment of cardio-renal disease

Given the increasing evidence that the NP system appears to counter the detrimental effects of the RAAS and the SNS, therapeutic strategies aimed at restoring or enhancing the physiological function of the NP system would appear to be a logical approach to address the pathophysiological consequences of cardio-renal disease.

Restoring or enhancing NP levels can be achieved by administration of exogenous NPs. In addition, inhibiting the enzyme NEP will also enhance NP levels. Although in theory, attenuating the clearance of NPs via blockade of the NPR-C might also augment NP levels, this is beyond the scope of this review and will not be discussed further.

5.1. Administration of exogenous natriuretic peptides

5.1.1. M-atrial natriuretic peptide

The human recombinant form of ANP, carperitide, was approved for the treatment of acute decompensated HF in Japan almost 20 years ago [11]. However, the short half-life of carperitide restricted its routine use, prompting the design and development of novel forms of ANP that are more resistant to enzymatic degradation than both native and recombinant forms [97]. M-ANP is a recently developed designer NP based on native ANP, but with more resistance to enzymatic degradation [97]. In vivo studies in canines have demonstrated that M-ANP possesses a greater ability to lower BP, enhance renal blood flow and GFR (despite reductions in BP), mediate natriuresis and diuresis, and suppress the RAAS compared with native ANP [97]. Similar findings were shown with M-ANP in an in vivo canine model of acute hypertension involving continuous infusion of Ang II [97]. Furthermore, the cardio-renal actions of M-ANP were compared with those of nitroglycerin in an in vivo canine model of HF and acute hypertension [98]. While both agents lowered mean arterial pressure and pulmonary wedge pressure from baseline, M-ANP was shown to potentiate renal function by significantly increasing GFR, renal blood flow, and natriuresis with significant inhibition of aldosterone activation; nitroglycerin had no significant impact on renal function or on aldosterone activation [98]. Clearly, the ability of M-ANP to lower BP and enhance renal function makes exploration into its potential to address cardio-renal disease very appealing. M-ANP has now entered clinical trials for further testing.

5.1.2. Nesiritide

Initial studies demonstrated that infusion of nesiritide, the recombinant form of human BNP, decreased pulmonary capillary wedge pressure, provided greater improvements in global clinical status and further reduced dyspnea and fatigue versus placebo [99]. Nesiritide was subsequently approved for the treatment of acute decompensated HF in the USA in 2001 [11]. However, reports of an increased risk of worsening renal function and death compared with control therapy raised questions over the safety of nesiritide [100,101]. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial subsequently demonstrated that nesiritide had no impact on the rate of death, nor was it associated with worsening renal function [102]. However, nesiritide was associated with increased rates of hypotension, which, together with its short bioavailability, has most likely had a negative impact on the routine use of the drug in clinical practice [45,102]. Of interest, data from the first patient recruited to a safety and dose-finding pilot study investigating low-dose nesiritide in patients with uncontrolled hypertension showed that nesiritide provided sustained BP-lowering actions in the absence of concomitant standard antihypertensive therapy [103].

5.1.3. CD-natriuretic peptide (or cenderitide)

CD-natriuretic peptide (CD-NP) or cenderitide belongs to the new breed of designer NPs. It is formed from the fusion of native human CNP with a C-terminal sequence of *Dendroaspis* NP (DNP) found in snake venom [104,105]. Crucially, CD-NP is less susceptible to degradation by NEP than native NPs [106]. In a canine model, CD-NP elicited potent natriuretic and diuretic responses, increased GFR, inhibited renin and induced less hypotension than BNP [104]. The antifibrotic actions of CD-NP have been demonstrated in vivo in an experimental rat model of early cardiac fibrosis [107]. CD-NP in vitro activated cGMP and suppressed cell proliferation of human cardiac fibroblasts induced by cardiotrophin-1 (a marker of HF and myocardial infarction) [104]. Recent research has proposed that CD-NP-eluting polymeric films may eventually be employed as cardiac patches which, via local application, could be used to suppress cardiac remodeling and fibrosis [108]. The first clinical trial in healthy human volunteers reported that CD-NP was well tolerated and activated cGMP, induced natriuresis, and suppressed aldosterone without causing excessive hypotension [109]. In patients with chronic HF, subcutaneous infusion of CD-NP has recently been shown to provide a dose-dependent reduction in systolic BP (SBP) and to be well tolerated [110]. CD-NP is currently undergoing Phase II clinical trials for chronic therapy in patients with post-acute HF [107].

5.1.4. CU-natriuretic peptide

An alternative version of CD-NP, known as CU-natriuretic peptide (CU-NP), has also shown early promise. CU-NP is constructed using a core component of native human CNP and the C- and N-termini of urodilatin, a NP of renal origin that predominantly interacts with the NPR-A [45,111]. Preliminary in vivo data in a canine model have suggested that CU-NP may mediate beneficial cardiac and renal effects, reducing pulmonary capillary wedge pressure and right atrial pressure (without systemic hypotension), inducing natriuresis, increasing GFR and suppressing the RAAS [112].

5.2. Inhibition of the degradation of natriuretic peptides by neprilysin

5.2.1. Neprilysin inhibitors

Candoxatril is an orally active NEP inhibitor [113]. By inhibiting NEP and so enhancing levels of NPs, candoxatril would be expected to enhance the hemodynamic actions of NPs, so potentially delivering benefit in the treatment of hypertension. However, in a study to examine the efficacy and tolerability of candoxatril in patients with hypertension, the BP-lowering efficacy produced by candoxatril was shown not to be clinically meaningful despite a significant increase in ANP [113]. It is known that NPs are not the only natural substrate for NEP — in addition to degrading NPs, NEP degrades other vasoactive peptides including vasodilators (e.g. substance P and bradykinin) and vasoconstrictors (such as Ang II and ET-1) [47–51]. A later study in patients with hypertension established that NEP inhibition with candoxatril leads to a significant increase in Ang II compared with placebo, and the authors concluded that the BP-lowering effects achieved with candoxatril alone may be offset by enhanced RAAS activity [114]. Furthermore, the overall BP response with NEP inhibition alone in patients with hypertension may depend on the relative balance between vasoconstrictor and vasodilator effects [114].

5.2.2. Vasopeptidase inhibitors

Based on these findings, it seems a fair assumption that the potential clinical benefits from NEP inhibition may only be fully realized if the RAAS is suppressed simultaneously. To address this, omapatrilat, the first in a new class of vasopeptidase inhibitors that combined inhibition of angiotensin-converting enzyme (ACE) and NEP in one molecule was developed [115]. In the Omapatrilat Cardiovascular Treatment versus Enalapril (OCTAVE) Phase III study in patients with hypertension, omapatrilat produced additional reductions in BP compared with ACE inhibition with enalapril, indicating the benefits of concomitant NEP inhibition and RAAS suppression over RAAS suppression alone [116]. However, in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) Phase III study conducted in patients with chronic HF, despite a trend towards a reduced primary endpoint of combined risk of all-cause mortality or hospitalization for HF with omapatrilat, the vasopeptidase inhibitor was not deemed superior to enalapril alone [117]. Furthermore, omapatrilat was associated with a greater frequency of angioedema than angiotensin-converting enzyme inhibitor (ACEI) therapy in both studies [116,117]. Bradykinin is thought to be a key mediator of angioedema [118]. Together with ACE, aminopeptidase P (APP), NEP and dipeptidyl peptidase-4 (DPP-4) are responsible for the enzymatic breakdown of bradykinin, although NEP and DPP-4 are only thought to play minor roles in the process [119]. Omapatrilat inhibits ACE, APP and NEP, and it may be that affecting three of the four enzymes involved in bradykinin metabolism accounts for the increased incidence of angioedema observed with omapatrilat [119]. As a result, despite any potential efficacy benefits, the increase in angioedema associated with omapatrilat leads to its discontinuation.

5.2.3. Angiotensin receptor neprilysin inhibitors

In order to capitalize on the apparent clinical promise of omapatrilat, while avoiding the associated increased risk of angioedema, intensive research began to determine if simultaneous inhibition of NEP and suppression of the RAAS could still be achieved without significant disruption to bradykinin metabolism. As a result, a new agent LCZ696 is now in clinical development. LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) — a novel compound that delivers simultaneous inhibition of NEP and suppression of the RAAS via blockade of the AT_1 receptor [120,121] (Fig. 2). Oral administration of LCZ696 delivers systemic exposure to the NEP inhibitor prodrug AHU377 (which is further metabolized by esterases to the active NEP inhibitor LBQ657) and the angiotensin receptor blocker (ARB), valsartan [120]. A Phase II trial demonstrated the antihypertensive efficacy of LCZ696 in patients with hypertension [122]. LCZ696 provided significantly greater reductions from baseline in BP than similar doses of valsartan in patients with mild-to-moderate hypertension [122]. Of interest, the authors highlighted how the magnitude of the reductions in SBP with LCZ696 was considerably greater than that for diastolic BP (DBP) [122]. Given the more notable impact on SBP than DBP, LCZ696 may offer potential clinical benefits for the treatment of patients with systolic hypertension [122].

A similar Phase II study conducted in Asian patients with mild-to-moderate hypertension confirmed the BP-lowering efficacy profile of LCZ696, showing significant reductions in BP and pulse pressure versus placebo [123,124]. In both Phase II hypertension trials, LCZ696 was well tolerated with no incidence of angioedema [122,124]. This is not entirely surprising, for although blockade of the AT_1 receptor with ARBs is thought to cause some angioedema, the risk is far lower than that found with ACEIs [125]. Unlike omapatrilat, LCZ696 only inhibits NEP out of the four enzymes involved in bradykinin metabolism, crucially with no direct effects on either ACE or APP [120].

It is well recognized that SBP becomes more difficult to control with aging [126], with systolic hypertension representing the predominant risk factor for adverse outcomes as patients age [127]. The aorta and the large elastic arteries stiffen with advancing age and together with the accompanying progressive increase in SBP, render hypertension more resistant to treatment [128,129]. In turn, this can create the possible need for more aggressive intervention to lower SBP as patients grow older, increasing the risks associated with unwanted DBP lowering in this patient population [128–131]. LCZ696 has the potential to treat patients with systolic hypertension by delivering an effective reduction in SBP without a similar magnitude reduction in DBP. Furthermore, by providing greater reductions in SBP than DBP versus similar doses of valsartan, LCZ696 also reduces pulse pressure more effectively than

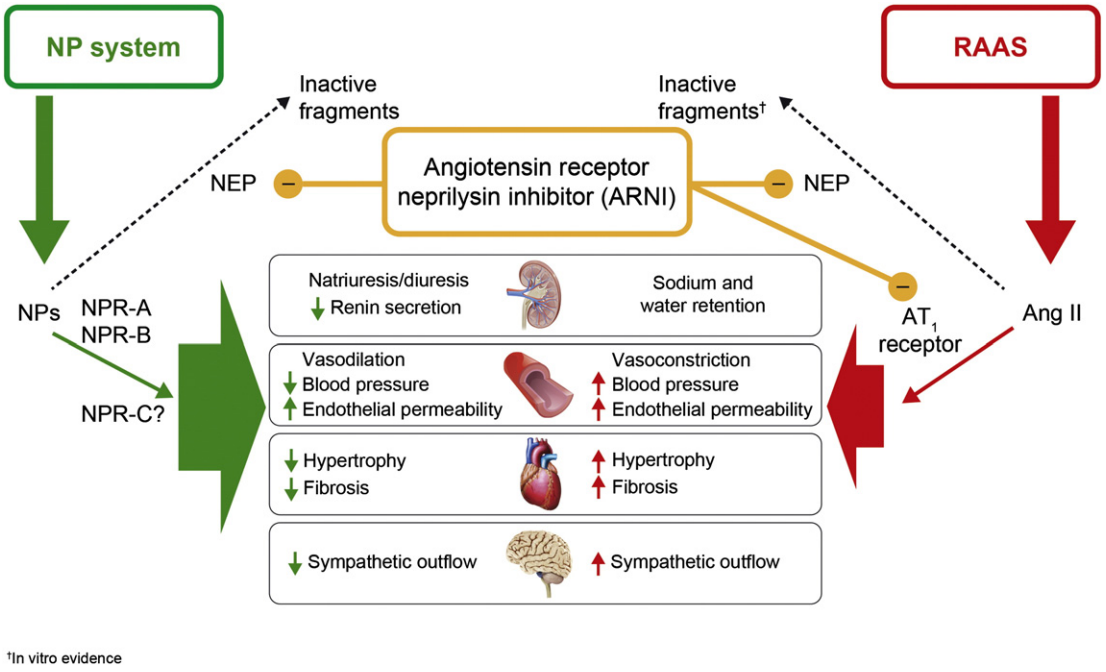

Fig. 2. Schematic representation to show the mode of action of an ARNI. NPs are degraded to inactive fragments by the enzyme NEP. Inhibition of NEP by an ARNI enhances NP levels, leading to biological effects that may have the potential to benefit CV health. However, Ang II is also a substrate for NEP, so NEP inhibition may lead to increased Ang II levels. Through blockade of the AT_1 receptor, an ARNI simultaneously suppresses the RAAS to counter the detrimental effects of elevated Ang II. Ang II = angiotensin II; ARNI = angiotensin receptor neprilysin inhibitor; AT_1 = angiotensin type 1 receptor; CV = cardiovascular; NEP = neprilysin; NP = natriuretic peptide; NPR = natriuretic peptide receptor; RAAS = renin–angiotensin–aldosterone system.

the ARB [122]. As pulse pressure is known to be an independent predictor of CV events [132], the significance of this finding with LCZ696 should not be underestimated. Interestingly, the Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker MEasuring arTERial stiffness in the elderly (PARAMETER) study will assess the efficacy of LCZ696 versus olmesartan on central aortic SBP and other measures of central hemodynamics and arterial stiffness in patients aged ≥60 years with increased SBP and wide pulse pressure [133].

LCZ696 has also been studied in patients with HF. The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial was a Phase II study that evaluated the efficacy and safety profile of LCZ696 compared with valsartan in patients with chronic HF and preserved ejection fraction (HFpEF) [134]. NT-proBNP, a marker of left ventricular wall stress associated with adverse outcomes in patients with HFpEF [135], was significantly reduced from baseline by LCZ696 compared with valsartan [134]. This study also assessed the effect of LCZ696 on left atrial structure and function by measuring left atrial width, volume and volume index [134]. An enlarged left atrium is a characteristic finding in patients with HFpEF and is reflective of sustained increases in left ventricular filling pressures. These parameters were significantly reduced from baseline to a greater extent in patients treated with LCZ696 compared with those treated with valsartan, indicative of reverse left atrial remodeling [134]. The tolerability profile of LCZ696 was favorable and similar to that with valsartan [134]. Meanwhile, the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial is a recently reported Phase III study that assessed the effect of LCZ696 on outcomes compared with enalapril in patients with HFrEF [136].

5.2.4. Endothelin-converting enzyme/neprilysin inhibitors

A further potential strategy targets ET-1 which, similar to Ang II, is a potent vasoconstrictor and pro-inflammatory peptide implicated in the development of CV disease [137]. ET-1 is derived from inactive big ET-1 by the actions of endothelin-converting enzyme (ECE) [138]. Agents that provide concomitant inhibition of ECE and NEP offer the potential to block the detrimental effects of ET-1 while enhancing the beneficial physiological effects of NPs [138]. Daglutril is a novel potent inhibitor of ECE and NEP, and has undergone Phase II clinical trial testing [138]. Recent evidence has indicated that in patients with type 2 diabetes and nephropathy, daglutril demonstrated effective BP-lowering (despite no significant effect versus placebo upon the primary endpoint of 24-hour urinary albumin excretion) [139]. Cardioprotective effects of SLV338, another ECE/NEP inhibitor under investigation, have also been reported in a study conducted in a rat model of renovascular hypertension [140]. SLV338 prevented cardiac hypertrophy, fibrosis and vascular remodeling in a BP-independent fashion [140]. In addition, beneficial renoprotective effects of SLV338 have been demonstrated in rat models of acute and chronic kidney failure, reducing mortality and preventing renal tissue damage [141]. Further investigations are warranted to uncover the full potential of ECE/NEP inhibitors in the treatment of cardio-renal disease.

6. Summary

Despite the mechanical function performed by the heart, it is essentially an endocrine organ which, in response to overload and cardiac stretch, releases NPs as a form of endogenous 'natural defense mechanism' to induce beneficial CV effects such as vasodilation, natriuresis and diuresis, and thereby maintain CV homeostasis. Additional autocrine and paracrine activities of the NP system, including the regulation of cardiac and vascular remodeling, and the control of energy homeostasis, further contribute to the positive influence of the NP system on key organs and tissues throughout the body.

Our understanding of the pathophysiology of cardio-renal disease is continually evolving. To date, inappropriate activation of the RAAS and SNS has been considered as the principal causal factor; however, evidence is now accumulating to suggest that disruption of the NP system also plays a key role in the pathogenesis of disease. As a result, strategies aimed at restoring or enhancing the NP system are coming to prominence, with the aim of capitalizing on the beneficial physiological effects

of NPs to maintain and restore CV health. NEP inhibitor monotherapy failed to produce clinically meaningful BP reductions, most likely due to an accompanying increase in Ang II levels. A more sophisticated approach involved simultaneous inhibition of NEP and suppression of the RAAS. The vasopeptidase inhibitors delivered effective BP reductions, but their clinical promise was limited by an increased incidence of angioedema. The angiotensin receptor neprilysin inhibitor, or ARNI, represents a favorable approach to inhibit NEP and suppress the RAAS via blockade of the AT_1 receptor, without the increased risk of angioedema. LCZ696, the first-in-class ARNI, has already demonstrated BP-lowering efficacy in patients with hypertension, in particular with respect to SBP, and improves cardiac biomarkers and remodeling in patients with HF. LCZ696 also has a favorable tolerability profile, both in patients with hypertension and those with HF. As the findings from ongoing and future planned studies with LCZ696 become known, more comprehensive conclusions can be made regarding the promising therapeutic potential of LCZ696 in addressing cardio-renal disease.

This paper has been based on a review of the literature conducted using PubMed. The only search criteria applied was to restrict articles to those published in English. Therefore, a possible limitation of this review is that it is based on the findings from a literature search conducted without a more formal structure, and so lacking explicit search inclusion and exclusion criteria.

Moving forward, interest in agents that modulate the NP system seems set to expand. Clearly this will not only enhance our understanding of the beneficial physiology of NPs, but it should also help reveal the full extent of how disruption of the NP system contributes to the pathophysiology of cardio-renal disease.

Conflict of interest

MV has received limited honoraria and travel expense reimbursement by Novartis Pharma AG for participating in expert board meetings related to the topic of this review paper.

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