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Review

Evolving use of natriuretic peptide receptor type-C as part of strategies for the treatment of pulmonary hypertension due to left ventricle heart failure

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ABSTRACT

Pulmonary hypertension (PH) due to left ventricular heart failure (LV-HF) is a disabling and life-threatening disease for which there is currently no single marketed pharmacological agent approved. Despite recent advances in the pathophysiological understanding, there is as yet no prospect of cure, and the majority of patients continue to progress to right ventricular failure and die. There is, therefore an urgent unmet need to identify novel pharmacological agents that will prevent or reverse the increase in pulmonary artery pressures while enhancing cardiac performance in PH due to LV-HF. In the present article, we first focused on the Natriuretic Peptide Receptor type C (NPR-C) based therapeutic strategies aimed at lowering pulmonary artery pressure. Second, we reviewed potential NPR-C therapeutic strategies to reverse or least halt the detrimental effects of diastolic dysfunction and impaired nitic oxide signalling pathways, as well as possibilities for neurohumoral modulation.

1. Introduction

Pulmonary hypertension (PH) is a serious and deadly clinical entity, which may be secondary to pulmonary vascular disease, chronic left heart or lung diseases, pulmonary embolism, or other miscellaneous conditions. Among the various groups of PH, PH due to left ventricular heart failure (LV-HF) represents by far the most common form of PH [1]. Although the exact prevalence of PH due to LV-HF is not well defined, most echo-based series suggest that 70% of PH may be caused by LV-HF [2]. Recognition of PH due to LV-HF is important because it is clearly associated with increased morbidity and mortality compared with LV-HF without PH [3]. In a large cohort of patients with LV systolic dysfunction, the presence of PH was associated with increased five-year mortality, independent of the severity of diastolic and systolic dysfunction, mitral regurgitation, or cardiovascular comorbidities [4]. The observed increased morbidity and mortality in patients with PH due to LV-HF appears to be related to the development of right ventricular (RV) dysfunction or failure. In a large cohort of HF with reduced ejection fraction patients, subjects with PH and reduced systolic function of the RV had the worst prognosis [5]. Similarly, in a prospectively identified community-based study of HF with preserved ejection fraction patients, RV dysfunction was common and was independently associated with all-cause mortality [6]. The combination of PH and RV dysfunction is therefore associated with disease progression, decreased exercise tolerance, and represents the strongest predictor of death [1]. In spite of advances in the understanding of the pathobiology of PH due to LV-HF, there is as yet no prospect of cure of this devastating disease and most patients continue to progress to RV failure and die [2]. In addition, there is no single medical treatment currently approved for PH due to LV-HF. Whereas targeted treatments are available for pulmonary arterial hypertension (PAH) [7], these therapies are not indicated and may even be harmful in patients with PH due to LV-HF [8]. The failure of to date therapeutic strategies suggests that important pathogenic cellular and molecular mechanisms have neither been identified nor therapeutically targeted [8].

2. Pathobiology of pulmonary hypertension due to left ventricular heart failure

Left ventricular heart failure (LV-HF) remains the most common cause of PH (henceforth described as PH due to LV-HF). PH due to LV-HF may occur in patients with HF with reduced ejection fraction, HF with preserved ejection fraction, or HF caused by left-sided valvular heart disease. The primary hemodynamic insult that results in isolated post-capillary PH (Ipc-PH) in subjects affected by PH due to LV-HF is an elevation in intracardiac or LV filling pressures. In addition, a significant number of patients

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with LV-HF may develop secondary (or functional) mitral regurgitation as a result of LV systolic or diastolic dysfunction, which in turn may worsen Ipc-PH. The overall increased LV filling pressures may reduce pulmonary arterial compliance promoting "stiff" pulmonary vasculature, which in turn may lead to enhanced pulmonary wave reflections during systole as well as an elevated pulsatile load on the RV [9]. In this so-called "passive" form of PH or Ipc-PH, pulmonary vascular resistance (PVR) may not be increased. Worsening LV-HF is often associated with worsening PH, and presumably, one will often exacerbate the other [1]. The subset of patients with PH due to LV-HF with combined post- and precapillary PH (Cpc-PH) may develop pulmonary arterial disease secondary to vasoconstriction and pathologic remodelling of the pulmonary vasculature ("reactive form of PH"). In patients with Cpc-PH, the elevation in the mean pulmonary artery pressure may be more excessive than that generated by the transmission of increased LV filling pressures alone (often referred to as "out-of-proportion" PH). Evidence suggests it may be this chronic backward transmission of increased intracardiac pressures which drives the whole process leading to maladaptive changes in pulmonary vessel wall composition and pulmonary vascular tone [10]. Histologically, some of these patients may have pulmonary vessels with evidence of medial hypertrophy, intimal fibrosis, and in-situ thrombosis, though plexiform lesions, a hallmark of idiopathic PAH are rarely seen [11, 12]. It is during the transition from normal to remodelled pulmonary vasculature that occur crucial pathophysiologic processes including changes in key metabolic pathways, from which the nitric oxide (NO) pathway is believed to be a major contributor to its homeostasis [10]. Recent studies have, therefore, focused on targeting the NO pathway in patients with PH due to LV-HF, however they all failed to reach their primary endpoints [1]. This was an expected outcome as HF patients are known to have endothelial dysfunction and thus reduced or loss of NO signalling pathway [10, 13, 14]. Interestingly, evidence also suggests that in the presence of a reduced or loss of NO signalling pathway, there may be an enhanced natriuretic peptide (NP) clearance receptor (NPR-C)-mediated vasorelaxant effect [10, 13, 14]. They may therefore be some synergistic and complementary cardioprotective roles for NPR-C signalling and NO-mediated signalling in the pulmonary vasculature [10, 13, 14]. The inhibition of one signalling pathway may thus be compensated for by the upregulation of the other [10, 13, 14]. These observations raise the intriguing question of whether NPR-C signalling pathway may play a critical role in PH due to LV-HF pathobiology, and thus representing an attractive therapeutic target [10].

3. Natriuretic peptide receptor type-C (NPR-C) based strategy for PH due to LV-HF

3.1. Background

3.1.1. Historical background

Most of the biological actions of Natriuretic Peptides (NPs), including atrial (ANP), B-type (BNP), C-type (CNP) and dendroaspis (DNP) appear to be mediated by attachment to three distinct receptors on the cell membrane, denoted NP receptors A, B and C (NPR-A, NPR-B, and NPR-C) [15, 16]. As illustrated in Fig. 1 [15], binding of NPR-A (which binds ANP and BNP) and NPR-B (which only binds CNP) may result in activation of a membrane bound guanylyl cyclase (GC) enzyme and subsequent generation of intracellular cyclic guanosine monophosphate (cGMP), which may mediate most of the biological actions of NPs [15]. NPR-C, which binds all natriuretic peptides with similar affinity, does not contain a GC domain and was originally classified as a 'clearance receptor' with no signalling function. Although still commonly called a clearance receptor (and thus largely ignored) [15] recent studies have shown that NPR-C is coupled to a pertussis toxin sensitive [17] inhibitory G protein (G_i) and mediates a reduction in adenylyl cyclase (AC) activity and intracellular cAMP levels [18]. In order to better understand the *functions* carried out by NPR-C within the cardiovascular system, the generation of a *knockout* mouse is a powerful strategy to characterize its roles within the hearts. (See Fig. 2.)

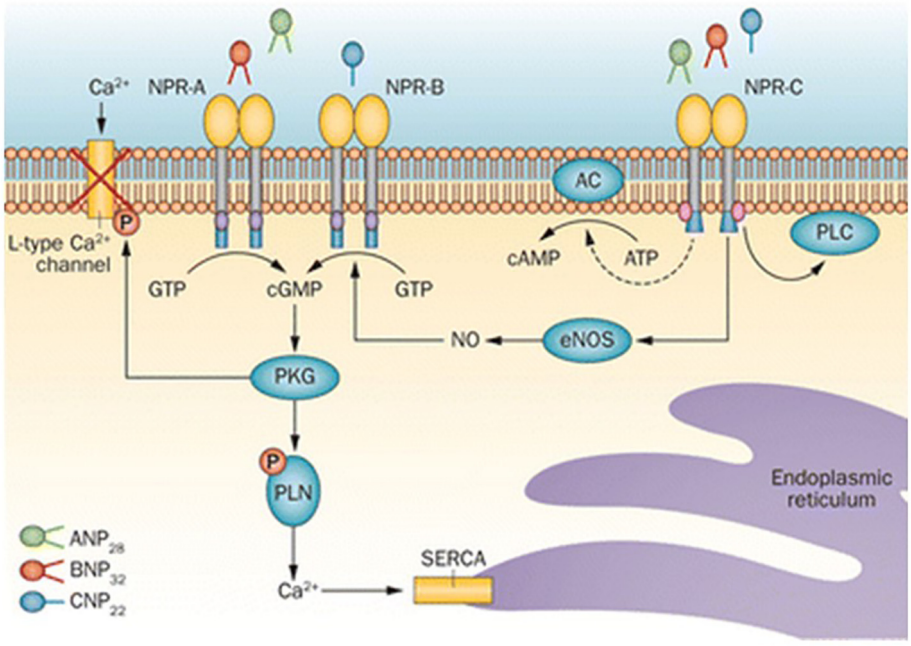

Fig. 1. The natriuretic peptides exert their effects through transmembrane receptors: NPR-A, NPR-B, and NPR-C. NPR-A and NPR-B are guanylyl cyclases, which catalyze the synthesis of cGMP from GTP. In vascular and cardiac cells, the intracellular effects of these receptors are mediated through PKG phosphorylating downstream targets such as PLN, which is an important regulator of intracellular Ca^{2+} concentrations by mediating Ca^{2+} sequestration in the endoplasmic or sarcoplasmic reticulum and downregulation of the L-type Ca^{2+} channels located in the cell membrane. The NPR-C lacks guanylyl cyclase activity; instead, receptor activation is coupled to inhibition of AC or activation of PLC. Moreover, indirect cGMP signalling downstream from NPR-C occurs through activation of eNOS. Abbreviations: *AC*, adenylyl cyclase; *ANP*, atrial natriuretic peptide; *BNP*, B-type natriuretic peptide; *cAMP*, cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; *CNP*, C-type natriuretic peptide; *eNOS*, endothelial nitric oxide synthase; *GTP*, guanosine triphosphate; *NO*, nitric oxide; *NPR*, natriuretic peptide receptor; *P*, phosphorylation; *PKG*, cGMP-dependent protein kinase 1 (also known as protein kinase G); *PLC*, phospholipase C; *PLN*, phospholamban; *SERCA*, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase.

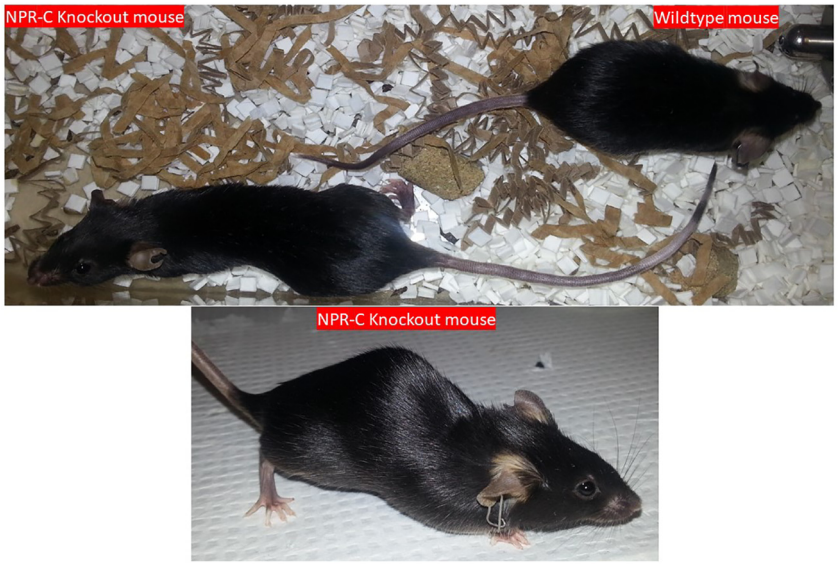

Fig. 2. Phenotypes of NPR-$C^{+/+}$ and NPR-$C^{-/-}$ mice. (a) Wild-type (right) and (b) knockout mice (left and bottom) at 15 weeks of age. NPR-$C^{-/-}$ mice are easily distinguished from their wild-type counterparts NPR-$C^{+/+}$ by a striking hunched back, an increase in body length despite a smaller thoracic cage and an elongated tail.

3.1.2. Phenotype of mice lacking NPR-C

Evidence suggests that the *NPR3* gene encoding for NPR-C receptor may be a causative gene for skeletal abnormalities. In an elegant experiment to investigate how NPR-C affects the cardiovascular and renal systems, Matsukawa and colleagues inactivated the Npr3 gene in mice by homologous recombination in embryonic stem cells [19]. Unexpectedly, the authors found that NPRC knockout mice (NPR-$C^{-/-}$) exhibit striking skeletal deformities [19]. As illustrated in Fig. 1, NPR-$C^{-/-}$ mice are easily distinguished from their wild-type counterparts (NPR-$C^{+/+}$) as early as 7 days of age by a dome-shaped skull, a striking hunched back, an increase in body length despite a smaller thoracic cage and an elongated tail [19]. Interestingly, these skeleton abnormalities are similar to the phenotype of mice with mutations in the gene encoding a bone morphogenetic protein type 2 receptor (BMPR2) [20, 21], which is the major genetic factor that promotes the development of idiopathic PAH (iPAH) [21]. In fact, compelling evidence does suggest that individuals affected by iPAH may exhibit intrinsic morphological and functional musculo-skeletal abnormalities, which may limit their exercise capacity [22]. Although cardiac dysfunction is thought to be the main cause of exercise intolerance in patients with PAH, recent studies suggest that the contribution of peripheral muscle dysfunction to their exercise limitation may be quite significant [23].

3.1.3. Cardiac characterization of mice lacking NPR-C: A new animal model for PAH

We recently characterized the cardiac structure and function of NPR-$C^{-/-}$ mice by echocardiography [8, 24]. Mice lacking NPR-C exhibit right atrial dilation, hypertrophy of the right ventricular free wall and trabeculae, tricuspid regurgitation as well as echocardiographic findings suggestive of right ventricular pressure overload, including flattening and paradoxical bulging of the septum into the left ventricle during systole, which are all findings typically seen in humans with PAH [8, 24]. Consistently, Doppler Echocardiography assessment revealed a significantly higher right ventricular systolic pressure compared with wild-type littermates [8, 24]. These findings were also confirmed by resting right heart catheterization [8, 24]. Consistently, a down regulation of NPR-C in hypoxia-induced PAH has been reported, however this observation was repeatedly described as part of a compensatory mechanism of the lungs aimed at reducing NPs clearance from the circulation, thus enhancing the biological actions of NPs and mitigating the severity of hypoxia-induced PAH [8, 24, 25]. As illustrated in Fig. 3, the impaired NPR-C signalling pathway may be the result of several factors, including but not limited to an abnormal NPR3 gene, an inhibition of NPR3 gene expression, or an inhibition or abnormal NPR-C protein [25]. Of critical importance, evidence suggests that activation of NPR-C signalling pathway may have anti-proliferative effects [8, 24, 26]. Impaired activation of this signalling pathway may thus lead to failure of the antiproliferative effect of NPR-C in the pulmonary vasculature, which in turn results in vascular pulmonary injury, including endothelial dysfunction, vascular smooth muscle dysfunction, matrix changes, and platelets, as well as inflammatory cell activation [25]. The proliferation of smooth muscle in pulmonary arterioles, secondary to remodelling, would then ultimately lead to PAH [25]. As illustrated in Fig. 4, the imbalance between impaired activation and physiological activation may cause or prevent the development of PAH [25]. While an impaired activation of NPR-C signalling pathway may lead to PAH, the activators to NPR-C pathway may initiate signalling that results in the inhibition of cell proliferation in pulmonary artery smooth muscle cells and therefore reverses the remodelling that is typical to PAH [25].

3.2. Treatment strategies

Strategically, the treatment of PH due to LV-HF should be directed at optimising HF treatment as well as lowering the pulmonary artery pressure as this is the cause of RV dysfunction and failure. The treatment of HF has improved substantially in recent years [27]. However, Patients with PH due to LV-HF continue to progress to RV failure and die. Ultimately, RV dysfunction and function determine the prognosis of patients with HF [28]. Therapeutic strategies aiming at lowering pulmonary artery pressure and thus preserving or improving RV function are, therefore, required.

3.2.1. Effect of NPR-C agonists on pulmonary artery pressure

The first and most crucial step to preserve or improve RV function is to normalise the RV effective arterial elastance. Evidence suggests that the RV may recover its normal shape and function with afterload reduction to about normal levels [29]. Interestingly, we recently reported, for the first time, that a specific NPR-C's agonist, the ring-deleted atrial natriuretic peptide analogue, cANF4–23 (cANF) may reduce the right ventricular systolic pressure and the pulmonary artery systolic pressure as well as enhancing cardiac performance, including left ventricular inotropy, in an experimental model [1]. Interestingly, the effect of cANF on right ventricular systolic pressure and the pulmonary artery

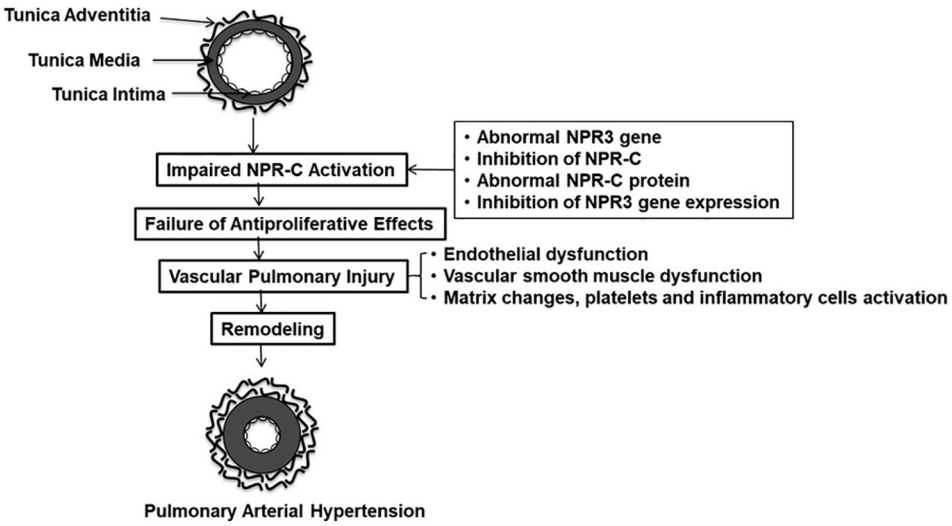

Fig. 3. Illustrates a schematic representation of a cascade of events following an impairment of NPR-C signalling pathway. The impaired NPR-C signalling pathway may be the result of several factors, including but not limited to an abnormal NPR3 gene, an inhibition of NPR3 gene expression, or an inhibition or abnormal NPR-C protein. Impaired activation of this signalling pathway leads to failure of the antiproliferative effect of NPR-C in the pulmonary vasculature, which in turn results in vascular pulmonary injury, including endothelial dysfunction, vascular smooth muscle dysfunction, matrix changes, and platelets, as well as inflammatory cell activation. The proliferation of smooth muscle in pulmonary arterioles, secondary to remodelling, would then ultimately lead to PAH.

systolic pressure was more striking in the age matched diabetic mice [1]. The increase in the magnitude of the right ventricular systolic pressure's reduction was attributed to the concomitant presence of endothelial dysfunction in diabetic mice [1]. As already hinted, in the vasculature, the vaso-relaxant effect of NPR-C signal transduction may be increased in the presence of NO synthase inhibition [1, 13, 14]. This may be of particular clinical significance in patients with PH due to LV-HF who are known to have endothelial dysfunction and thus reduced or loss of NO pathway [1, 13, 14].

3.2.2. Diastolic dysfunction

The chronic backward transmission of increased intracardiac pressures, which drives the whole process leading to the development of PH, may occur via two major cardiac mechanisms including (i) systolic

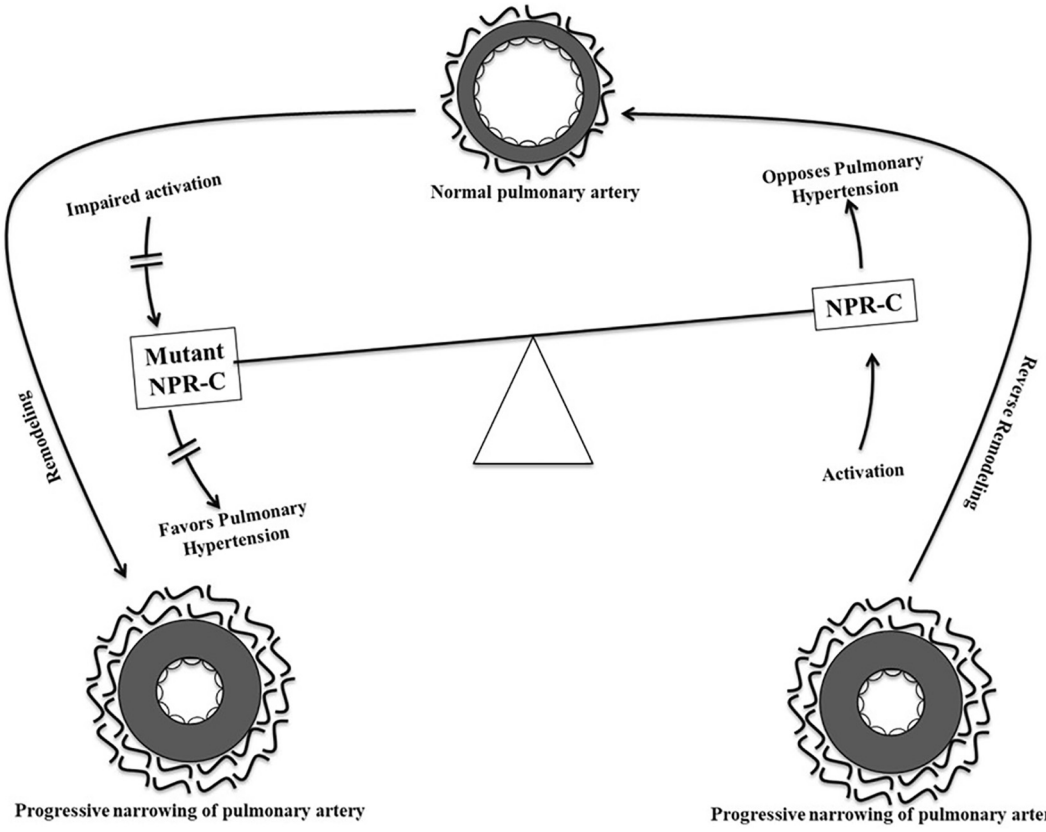

Fig. 4. Illustrates the loss of homeostasis with NPR-C signalling pathway. The imbalance between impaired activation and physiological activation may cause or prevent the development of PAH. Impaired activation of NPR-C signalling pathway leads to failure of the antiproliferative effect of NPR-C in the pulmonary vasculature, which in turn results in PAH. Activators to NPR-C pathway initiate signalling that results in the inhibition of cell proliferation in pulmonary artery smooth muscle cells and therefore reverses the remodelling that is typical to PAH.

dysfunction, in which there is impaired contractile function of the myocardium, and (ii) diastolic dysfunction, in which there is abnormal relaxation and increased stiffness of the myocardium. The majority of patients with PH have, however, normal LV ejection fraction (EF), and LV function may not be prognostic [30]. In fact, evidence suggests that PH development may be associated with an increased mortality/morbidity beyond that of LV dysfunction alone [31]. Consistently, Miller and colleagues have elegantly demonstrated that the development of PH in LV-HF is largely determined by the presence and the severity of diastolic dysfunction [32], which in turn appears to predict functional capacity and clinical worsening in PH [33]. While specific therapies have proved to be beneficial in systolic dysfunction, no such treatment strategies exist for diastolic dysfunction. To date the optimal strategy for treating diastolic dysfunction, of any level of severity, remains to identify and therapeutically target any underlying pathological conditions that contribute to it. Conceptually, pharmacological agents that could promote the regression of hypertrophy and fibrosis, and thus facilitate myocardial relaxation and/or improve LV compliance would be ideal for the treatment of diastolic dysfunction. Based on what has already been discussed above, and as we will further dissect in subsequent portions of this article, the NPR-C's agonists appear to have all the desired pharmacological properties that would make them the best drug candidates for the treatment of diastolic dysfunction. Interestingly, genetic alterations in the gene coding for NPR-C have been independently associated with the development of diastolic dysfunction in a random large cohort of residents from Olmsted County (Minnesota, USA), suggesting the potential and crucial role of NPR-C signal transduction in the pathophysiology of this capricious condition [34]. Most important, the authors found that the development of diastolic dysfunction was independent of age, sex, BMI and arterial hypertension in the homozygotes for this NPR3 genotype with an odds ratio of 1.9 similar to that of arterial hypertension, a major risk factor for diastolic dysfunction [34]. The mechanisms of the development of diastolic dysfunction in this cohort may be due, at least partially, to some alterations in the NPR-C's cytoplasmic domain within cardiac cells contributing to myocardial fibrosis and impaired diastolic function [1, 8, 34, 35]. NPR-C are well known to be expressed in various cardiovascular cell types including but not limited to cardiomyocytes, cardiac fibroblasts, vascular smooth muscle cells and endothelial cells [1, 8, 15, 16, 35]. Of critical importance and as hinted above, accumulating evidence does suggest that activation of NPR-C signal transduction may have anti-proliferative effects [1, 8, 26, 35].

3.2.3. Neurohumoral modulation

In patients with PH due to LV-HF, there may be an overactivity of the sympathetic nervous system. The sympathetic adrenergic stimulation may be required as first response to keep the RV coupled to the increased pulmonary artery pressure. In the long run, however, this may exert unfavourable cardiovascular, renal and metabolic effects [36]. With chronic sympathetic activation, the beta-adrenergic receptors may become downregulated, and this in turn may result in impaired myocardial contractile performance of the ventricles [29]. Patients with PH due to LV-HF may thus not get the full benefit of beta-blocking therapies as the beta-adrenergic receptor density may be reduced. The beneficial effects of beta-blockers is well established in HF, and may occur mainly via the dual actions of adrenergic receptor protection and heart rate (HR) reduction [15]. Evidence suggests that under basal conditions, BNP and CNP may, comparably, increase HR and electrical conduction via GC-linked NPR-A and NPR-B in experimental hearts and sino-atrial node (SAN) myocytes [37]. Both, BNP and CNP, may also increase action potential (AP) frequency in SAN myocytes from NPR-$C^{-/-}$ mice, as effectively as in those of NPR-$C^{+/+}$ mice, suggesting that BNP and CNP may function mainly through their GC-linked receptors, at least under basal conditions [15, 37]. Interestingly, the authors demonstrated that the increase of HR and SAN activities elicited by BNP and CNP may be blunted in the presence of a β-adrenergic stimulation [15, 38]. Importantly, the magnitude of this blunting effect was proportional to the degree of β-adrenergic stimulations [15]. These findings suggest that the native NPs may function via multiple NPs receptors simultaneously and their overall effects may vary in function of the degree of β-adrenergic stimulation [15]. These assumptions are supported by the evidence that with NPR-A blocked, BNP may reduce HR and SAN activity as effectively as cANF via NPR-C signalling but switched back to eliciting an increase in HR in NPR-$C^{-/-}$ hearts [15, 37, 38]. While NPR-A and NPR-B related signal transduction may mediate NPs effects under basal conditions and thus also probably in healthy individuals, NPR-C signalling pathway may be activated in conditions associated with high β-adrenergic stimulations such as HF [15]. Most importantly, its overall contributory effects may become progressively more prominent as the degree of β-adrenergic stimulation increases [15, 38]. Since NPR-C signalling may be upregulated in HF and its activation may act in a manner similar to β-blockers actions, pharmacological agents that also target this specific NPR-C may prove to be beneficial [15].

3.2.4. Coronary blood flow

Coronary vascular dysfunction may be highly prevalent among patients with PH due to LV-HF, which may be related to their functional class, as well as being independently associated with adverse cardiovascular events, including cardiovascular death, HF hospitalization, late revascularization, and aborted sudden cardiac death [39]. Restoration of coronary blood flow is therefore essential for limiting the damage caused by microvascular dysfunction and salvaging organ function. Although the mechanisms underlying coronary vascular dysfunction in patients with PH due to LV-HF are not well understood, evidence suggests that alterations in NO pathways may play a pivotal role in this process [40]. Unfortunately patients with PH due to LV-HF may have decreased NO bioavailability and endothelial dysfunction, which may limit the efficacy of therapeutic agents targeting NO signalling pathways [1, 8, 40]. Hence, considerable research attention has focused on identifying novel endogenous pathways and therapeutic interventions that may prevent or reverse coronary vascular dysfunction by targeting different mechanisms [41]. Interestingly, accumulating evidence suggest that NPR-C signal transduction may play a crucial role in the regulation of vessel tone and blood flow in the coronary vasculature, especially in the presence of endothelial dysfunction [1, 41]. Hobbs and others have demonstrated that not only enhanced NPR-C signal transduction may have vasorelaxant activity, but also its activation may protect against ischemia/reperfusion (I/R) injury by reducing infarct size [41, 42]. Interestingly, the vasorelaxant activity of NPR-C signal transduction may be significantly enhanced in the presence of a decreased or loss of NO bioavailability and endothelial dysfunction [41]. These observations suggest there may be complementary cytoprotective roles for NPR-C and NO signalling pathways in the coronary vasculature, whereby the loss of one signal transduction may be compensated for by the upregulation of the alternative signalling pathway [1, 41]. This is of particular clinical significance for patients with PH due to LV-HF because they are characterized by a decreased or loss of NO bioavailability and endothelial dysfunction [1]. As hinted above, accumulating evidence also suggests that NPR-C's agonists may protect the myocardium against the damaging effects of I/R injury by limiting the infarct size as well as the degree of the associated myocardial dysfunction [1, 8, 41]. Consistently, this cardioprotective effect was enhanced in the presence of a decreased or loss of NO bioavailability and endothelial dysfunction, indicating that the activation of NPR-C pathway may prove beneficial in patients with PH due to LV-HF [1, 8, 41, 43, 44]. Although the mechanisms for the NPR-C-mediated cardioprotective effects have not fully been elucidated, evidence does suggest this may, at least partially, be secondary to NPR-C induced G_i stimulation, which may in turn result in activation of the (G protein–gated) inwardly rectifying K^+ channels (K_{IR}), leading to hyperpolarization and relaxation of vascular smooth muscle cells [1, 8, 41–44]. Evidence also suggests that a reduction in K_{IR} channel activities may exacerbate I/R injury [45], and thus further providing indications that NPR-C mediated-preservation of K_{IR} channel function, may prove to be beneficial in minimizing I/R injury [41].

3.2.5. Erectile dysfunction

Erectile dysfunction (ED) is common in patients with HF, and some studies have reported that more than 90% of HF patients may have reduced libido and erectile problems, which seems to be independent of the New York Heart Association (NYHA) functional class [46]. These proportions may even be higher in patients with PH due to LV-HF. It is also well established that some of the standard HF medications including but not limited to beta-receptor blockers, thiazide diuretics and digoxin may worsen sexual dysfunction, which may, in turn, lead to medications non adherence in misguided efforts to maintain satisfactory sexual activity, with secondary worsening of PH due to LV-HF [46]. Hence, considerable research attention has also been focused on identifying novel therapeutic interventions that may preserve or reverse ED in this patient's population. Although the mechanisms of the development of ED in PH due to LV-HF may be multi-factorial, evidence suggests there may be alterations specific to PH due to LV-HF, which may be important contributors to ED. [46] For instance, inadequate vascular smooth muscle relaxation may represent the common final pathway leading to ED in PH due to LV-HF [46]. A dysregulation of vascular smooth muscle relaxation have been associated with impaired bioavailability of NO and endothelial dysfunction, raising again the intriguing question of whether the activation of the NPR-C signal transduction may prove to be beneficial in this context [40]. Kun and colleagues have demonstrated that the selective NPR-C agonist, cANF [4–23], may induce vascular smooth muscle relaxations in human penile small arteries via the activation of the K_{IR} channel [47]. Interestingly, the authors found that this vasodilation effect was significantly more pronounced in the presence of a decreased or loss of NO bioavailability and endothelial dysfunction, further indicating that the activation of NPR-C pathway may also prove beneficial for ED in patients with PH due to LV-HF [47].

4. Summary

We reviewed the potential NPR-C based strategies for the treatment of PH due to LV-HF. The preservation of the RV may play a crucial role in the progression of the RV towards dysfunction and failure. Therefore, we first focused on NPR-C based therapeutic strategies aimed at lowering pulmonary artery pressure. As wall stress is a major determinant of myocardial oxygen consumption, a reduction in RV afterload may also have a positive impact on myocardial oxygen delivery (preservation of RV wall thickness) and consumption for energy metabolism. Second, we reviewed potential NPR-C therapeutic strategies to reverse or least halt the detrimental effects of diastolic dysfunction and impaired NO signalling pathways including coronary and erectile dysfunctions. The role of NPR-C on neurohumoral modulation is challenging and requires further investigations. Although evidence for NPR-C based strategies for the treatment of PH due to LVF are attractive, further research is still needed before clinical application can be pursuit. In conclusion, NPR-C should now be considered as a critical protective receptor in the heart rather than just being a clearance receptor.

Disclosures

None.

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