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Review

Neprilysin inhibitors: A new hope to halt the diabetic cardiovascular and renal complications?

Vajir Malek, Anil Bhanudas Gaikwad*

Laboratory of Molecular Pharmacology, Department of Pharmacy, Birla Institute of Technology and Science Pilani, Pilani Campus, Rajasthan 333031, India

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ABSTRACT

Diabetes is an enormous and ever-growing calamity and a global public health threat of the 21st century. Besides insulin and oral hypoglycaemic drugs, blockage of the renin-angiotensin system (RAS) denotes a key pharmacotherapy for the management of cardiovascular (CVD) and chronic kidney diseases (CKD), which are the leading causes of disability and death among diabetic patients. Neprilysin (NEP) inhibition, auxiliary to RAS blockage increases the bioavailability of natriuretic peptides and benefits the cardio-renal system. Omapatrilat, a dual angiotensin-converting enzyme (ACE) and NEP inhibitor has been reported to show superior anti-hypertensive, anti-atherosclerotic, insulin-sensitizing, cardiovascular and renoprotective effects to ACE inhibitors in experimental animal models for diabetes. In clinical trials on hypertensive subjects Omapatrilat increased the risk of angioedema due to which its further development as anti-hypertensive drug was hampered. This event prompted the development of angiotensin receptor neprilysin inhibitors (ARNi). The first representative of ARNi, LCZ696 (Sacubitril/Valsartan) halted cardiovascular and renal functional decline and hence protected against CKD and CVD. Recently, LCZ696 was approved by U.S. Food and Drug Administration for the treatment of heart failure. This concise review intends to summarise the currently available reports on NEPi as a therapeutic intervention to treat CVD and CKD associated with diabetes.

Contents

1. Introduction

Notwithstanding substantial improvements in diagnosis and treatment, diabetes remains a major public health concern. According to the global status report on non-communicable diseases 2014 by WHO, diabetes caused 3.7 million deaths in year 2012, and by year 2030 it will be the 7th leading cause of deaths

Abbreviations: ARBs, Ang II receptor blockers; AT2R, Ang II type 2 receptors; AT1R, Ang II type 1 receptors; Ang II, angiotensin II; ARNi, angiotensin receptor neprilysin inhibitors; ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CVD, cardiovascular diseases; CKD, chronic kidney diseases; CNP, C-type natriuretic peptide; HF, heart failure; NP, natriuretic peptide; NEP, neprilysin; NEPi, neprilysin inhibitors; RAS, renin-angiotensin system; STZ, streptozotocin; TGF-ß, transforming growth factor-ß; VPi, vasopeptidase-inhibitors.

* Corresponding author.
E-mail address: anil.gaikwad@pilani.bits-pilani.ac.in (A.B. Gaikwad).

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worldwide [1]. Among all the diabetic complications, cardiovascular diseases (CVD) and chronic kidney diseases (CKD) are the main culprits for morbidity and mortality [2,3]. The pathogenesis of diabetes associated CVD and CKD is complex and inter-linked with multiple transmembrane signalling cascades. Initial metabolic insults promoted by underlying genetic predisposition, hyperglycaemia, and hyperinsulinemia activate neurohormonal stressor systems like sympathetic nervous system, endothelin (ET) system and, the pressor arm [Ang II (angiotensin II)/ACE (angiotensin-converting enzyme)/AT1R (Ang II type 1 receptors)] of the renin-angiotensin system (RAS). The activation of neurohormonal systems is one of the consistent features in array of diseases like hypertension, heart failure (HF), stroke, CVD and CKD, and hence their blockade denotes a key therapeutic strategy in treatment of these diseases [4]. Along with the neurohormonal stressors, the human body has potent counter-regulatory systems such as natriuretic peptide (NP) system and the depressor arm [Ang (1–7)/ACE2/Mas receptors] of RAS, which lower the blood pressure and mediate multitude of beneficial effects in cardiovascular and renal system [5–8].

Neutral endopeptidase or neprilysin (NEP) hydrolyses NPs and modulates their structural and functional effects on heart, kidney and other organs [9]. The neprilysin inhibitors (NEPi) have been found to increase the level of protective NPs which in turn leads to their role in protection against diabetic complications. However, NEPi alone were insufficient to combat cardiovascular diseases as required by standard pharmacotherapy [6]. Based on the current understanding of neurohormonal systems, the dual acting inhibitors of neprilysin and pressor arm (Ang II/ACE/AT1R) of RAS have been developed and were found to be beneficial in curbing CVD and CKD in diabetic as well as non-diabetic conditions [4,10]. In experimental and clinical studies, the vasopeptidase inhibitors (VPi) (Combined ACEi/NEPi e.g. Omapatrilat) were found to be protective against hypertension, heart failure and CKD [5,11,12]. Despite the promising cardiovascular and renal protection, development of VPi was stopped due to increased frequency of angioedema [13–15]. These findings prompted the development of angiotensin receptor neprilysin inhibitors (ARNi), which syndicate the beneficial effects of Ang II receptor blockers (ARB) and NEPi with reduced risk of angioedema compared with combined ACEi/NEPi. LCZ696, the first representative of ARNi, is a combination of two moieties- an ARB (Valsartan) and a NEPi (Sacubitril). LCZ696 has been reported to improve cardiac functions and attenuate fibrosis through inhibition of transforming growth factor-ß (TGF-ß) in heart failure with reduced ejection fraction in streptozotocin (STZ) induced diabetic mice [16]. Optimum AT1 receptor- neprilysin inhibition by Thiorphan (NEPi) and Irbesartan (ARB) have superior cardioprotective effects as compared to AT1R blockade alone in hypertensive rats [17]. Importantly, same combination displayed better renoprotection than ARB alone in diabetic rats [18]. Abovementioned reports have highlighted ARNi as potential target for the management of diabetic complications. This review is aimed to present a detailed overview of standalone and combined NEPi for the management of diabetes and discuss its potential to halt cardiovascular and renal functional decline in diabetes.

2. Inhibition of renin angiotensin system in diabetes

The renin angiotensin system (RAS) is an important neurohormonal system from both physiological and pathological perspectives. The octapeptide, Ang II is main effector of RAS which controls structural and functional changes on heart, kidney, and vasculature. Ang II, generated from Ang I by the action of angiotensin-converting enzyme (ACE) majorly elicits its effects through Ang II type 1 receptors (AT1R) and Ang II type 2 receptors (AT2R). Ang II via AT1R upregulates many pro-inflammatory and pro-fibrotic gene [vascular cell adhesion molecule 1, intercellular adhesion molecule-1, interleukin-6, TGF-β, and plasminogen activator inhibitor-1] through the activation of several intracellular signalling cascades including the NF-κB, mitogen-activated protein kinase, and redox pathways, which play a crucial role in pathogenesis of hypertension, diabetes, atherosclerosis, renal failure and congestive heart failure [4,19–21]. Diabetes is a state of neurohormonal imbalance and enduring activation of RAS which in turn leads to chronic upsurge in Ang II, renin, and aldosterone levels. These peptides exert maladaptive effects on cardiovascular and renal system, and in long-term causes functional decline or impairment [22,23].

Hence, since past few decades, blockage of the pressor arm of RAS either by ARB or ACE inhibitors (ACEi) has been the ‘corner stone’ for management of CVD and CKD associated with diabetes [24,25]. Surprisingly, RAS blockers are generally prescribed to a diabetic individual without history of diabetes associated CVD, CKD or other complications because of their recognized prophylactic effects. A meta-analysis from various clinical trials carried out to investigate the effects of RAS blockage on diabetes reported that, early RAS interventions are more beneficial than late interventions in delaying end-stage renal disease in patients with type 2 diabetes [22]. However, recently some clinical studies and meta-analysis have reported that for diabetic patients’ treatment with ARB or ACEi do not offer any advantages over other antihypertensive medications [24,26,27]. In addition, ‘aldosterone escape’ and ‘Ang II reactivation’ have been observed during either ARB or ACEi pharmacotherapy which clinically manifested as copious water and salt retention, and reduction in glomerular filtration rate [28,29]. Aforementioned facts underscore the necessity of new therapeutic interventions for prevention and cure of CVD and CKD related to diabetes. A possible solution of this problem lies in an auxiliary approach by augmentation of endogenous blood pressure lowering and RAS opposing “natriuretic peptide system”.

3. Augmentation of natriuretic peptide system in diabetes

Natriuretic peptide (NP) system is a group of structurally related but genetically different hormones or paracrine factors, having actions that are targeted at protecting the cardiovascular system from volume overload. The mammalian NP system comprises of mainly three NPs: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), all of which share a common 17-amino acid ring structure [30,31]. The distribution and regulation of NPs are tissue specific and exclusive. ANP and BNP, primarily synthesized and released from the atria and left ventricle of heart, respectively, circulate as hormones to act on various body tissues (e.g. venous system, kidneys, and brain) and induce vasodilation, natriuresis, and diuresis, thereby helping in regulation of blood pressure, fluid and electrolyte balance [30,32]. In the kidney, more specifically distal tubular cells, expression of ANP precursor produces a subtype called urodilatin, which helps ANP to regulate renal sodium and water excretion through inhibition of antidiuretic hormone and, Ang II/aldosterone dependent sodium and water reabsorption (Fig. 1). In addition, NPs are known to oppose RAS and have anti-proliferative and anti-hypertrophic effects [30,31,33]. Other biological actions of NPs are depicted in Fig. 1.

Ever since the discovery of NPs by de Bold and colleagues, the scientists are striving to exploit the potential benefits of NPs for the management of CVD. The first way to increase NPs’ levels that struck the researchers was to administer it as an exogenous hormone. BNP exerts antihypertrophic effect in isolated heart of streptozotocin (STZ) induced type 1 diabetic male Sprague-Dawley