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Current role of neprilysin inhibitors in hypertension and heart failure ☆

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ABSTRACT

Cardiovascular diseases (CVD) continue to represent the major cause of death, morbidity and healthcare expenditure worldwide. Current medical therapy fails to effectively halt disease progression and to reduce adverse clinical outcomes, reflecting incomplete understanding of pathomechanisms as well as the need to expand current pharmacotherapeutic strategies. Hypertension and heart failure, the most important CVD entities, are associated with imbalance in neurohormonal systems activity such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system and the endothelin system. Blockade of the RAAS constitutes the most successful pharmacotherapeutic concept in hypertension and heart failure to date. The RAAS-opposing natriuretic peptide system constitutes the body's own BP-lowering system, and mediates a multitude of beneficial actions within cardiovascular tissues. The metallopeptidase neprilysin (NEP) hydrolyzes natriuretic peptides. Conceptually, NEP inhibition would increase salutary natriuretic peptide actions in CVD. Stand-alone NEP inhibitors (NEPi) lacked efficacy beyond standard pharmacotherapy. Combined blockers of NEP and the endothelin system demonstrated efficacy in preclinical studies but have not been evaluated in clinical trials. A decade ago, omapatrilat and other dual-acting NEPi-ACEi (vasopeptidase-inhibitors) were promising agents for hypertension and heart failure. Despite greater efficacy, development of vasopeptidase-inhibitors was halted due to significant off-target effects in some cohorts, most notably increased frequency of angioedema in hypertensive subjects. Novel angiotensin-receptor-neprilysin-inhibitors (ARNi) seek to fully exploit clinical efficacy of combined RAAS-blockade and NEPi-mediated natriuretic peptide augmentation, and hopefully so at improved clinical safety. We herein review current knowledge of NEPi as stand-alone and combined pharmacotherapeutic agents in hypertension and heart failure.

Contents

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1. Introduction

Despite significant improvements in the diagnosis and management the global health and socioeconomic burden of cardiovascular disease (CVD), in particular that of hypertension and heart failure (HF) remains a major public health concern (Roger et al., 2012; Heidenreich et al., 2013). Steep increases in prevalence of CV risk factors in developing countries as well as aging populations in the Western world are important contributing factors (May et al., 2012).

Approximately one in two adults have hypertension, and a significant proportion of hypertensive subjects are not treated to blood pressure targets recommended by guideline bodies. Elevated blood pressure remains frequently asymptomatic, yet, when ignored or undertreated may result in devastating consequences: hypertension is a major cause of HF, stroke, renal failure, blindness, and vascular complications such as acute aortic dissection. Novel evidence suggests that similar pathophysiological mechanisms drive end-organ damage across the spectrum of CVD such as hypertension and HF (Formentini et al., 2012).

Current pharmacotherapy for hypertension and HF may slow down disease progression but fails to completely reverse the underlying pathogenetic processes. For HF this is reflected by the fact that patients hospitalized for HF have poor long-term survival and substantial HF-related morbidity despite contemporary therapy (Jhund et al., 2009). The grim overall prognosis together with the projected rise in prevalence of CVD continues to stimulate research efforts into novel medical therapies.

One consistent feature throughout the continuum of CVD is activation of neurohormonal systems. Short-term these systems may initiate biologically meaningful "injury responses" (such as those triggered by blood loss) that stem from their "organism-conserving" role in evolution. However, sustained chronic overactivity of these systems often induces and maintains progressive CVD. The renin-angiotensin-aldosterone (RAAS) system, the sympathetic nervous system (SNS) and the endothelin (ET) system are such major important neurohormonal stressor systems that are capable not only of elevating blood pressure (BP) by retaining water and sodium but also of contributing to CVD pathophysiology (Haynes & Webb, 1998; Goldsmith, 2004; Parati & Esler, 2012; von Lueder & Krum, 2013). Thus, their blockade represents an important therapeutic paradigm. On the other hand, the human body possesses powerful counter-regulatory systems such as the natriuretic peptide system (NPS), a potent endogenous BP-lowering system that is associated with cardiovascular protection (Burnett et al., 1984; Munagala et al., 2004; Potter et al., 2006). Most neurohormonal systems contain enzymes involved in the metabolism of effector peptides modulating structural and functional effects on the CV system. Angiotensin-converting enzyme (ACE), neutral endopeptidase or neprilysin (NEP), and endothelin-converting enzyme (ECE) are such membrane-bound metallopeptidases that are widely distributed within CV tissues and cleave a multitude of substrates, suggesting them as possible attractive therapeutic targets to abrogate neurohormonal overdrive (Dive et al., 2009). The success of ACE-inhibitors (ACEi) in CVD therapy initiated development of similar strategies such as NEP (NEPi) and ECE (ECEi)-inhibitors both as single agents and as part of combined agents (von Lueder et al., 2013). Clinical development of single-acting NEPi was curtailed due to lack of efficacy as stand-alone BP-lowering agents (Roques et al., 1993; Cleland & Swedberg, 1998).

It was only with dual-acting NEPi strategies that the clinical benefit of NEPi was realized. Early compounds were the vasopeptidase-inhibitors (VPi) containing an ACEi with NEPi. VPi showed greater efficacy than standard medication in some hypertension and HF cohorts. However, VPi also led to an increased frequency of angioedema in some studies that was presumably caused by excessive bradykinin accumulation (Messerli & Nussberger, 2000).

Novel combined-NEPi were therefore designed to circumvent these specific problems while maintaining the clinical efficacy of dual blockade. The most recent compounds are angiotensin-receptor-NEP-inhibitors (ARNi) which are currently being evaluated in clinical studies (von Lueder et al., 2013).

We herein review the current evidence of stand-alone and combined NEP-inhibiting drugs in hypertension and HF, and discuss efficacy and safety aspects relevant to their potential clinical applicability.

2. Neprilysin (NEP), NEP inhibitors and the natriuretic peptide system in physiology and pathology

Neprilysin (NEP), also known as neutral endopeptidase, enkephalinase or endopeptidase EC24.11 is a zinc-dependent type II integral membrane metallopeptidase with ubiquitous distribution (see Fig. 1; modified from (Oefner et al., 2000)). NEP has greatest abundance in the kidney but is widely found in CV and other tissues. The most important biological function of NEP appears to be hydrolysis of the natriuretic peptides (NP) although a multitude of other NEP substrates exist. The latter include vasoactive peptides such as angiotensin-I (AngI), AngII, endothelin-1 (ET-1), kinins, adrenomedullin, opioid peptides, Substance P, amyloid β protein, enkephalin, and gastrin (Erdos & Skidgel, 1989; Yamamoto et al., 1992; Roques et al., 1993; Ferro et al., 1998; Campbell, 2003). This "promiscuity" of NEP towards multiple substrates provides an explanation for the fairly broad-based effects upon selective NEP inhibition.

The NPs are a family of peptides which are released by cardiac and renal tissues as a response to increased cardiac wall stress and volume overload, such as occurring in poorly-controlled hypertension and heart failure. The NPs include three related peptides, namely atrial (ANP), brain (BNP) and C-type (CNP) NP (see Fig. 2; modified from (Clerico et al., 2006)). The NPs stimulate renal secretion of water and

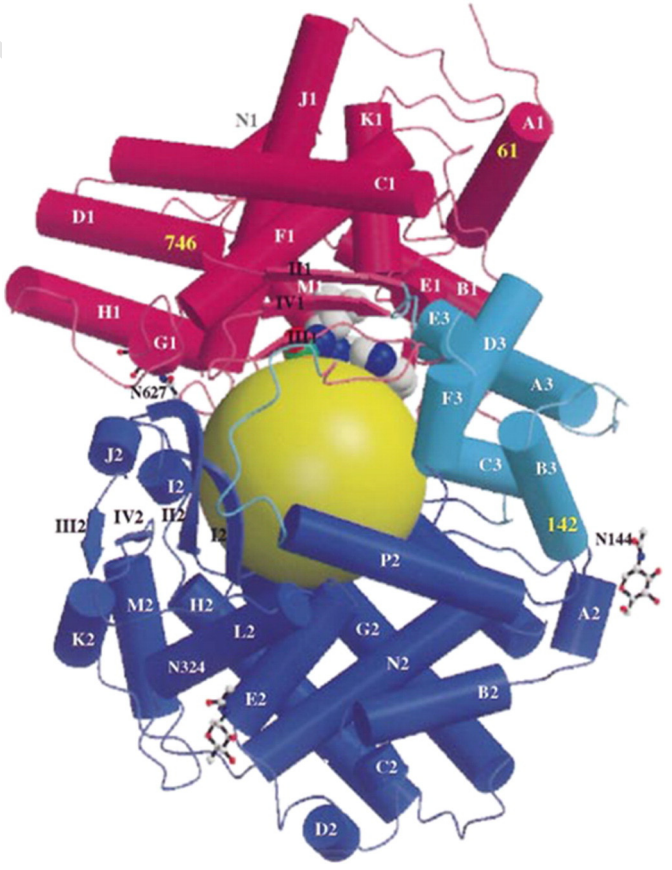

Fig. 1. Three-dimensional cartoon model of soluble NEP with the cavity of active site depicted in light green, domain 1 in purple and domain 2 in blue (reprinted with permission). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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