New Era of Antihypertensive Agents- Vasopeptidase Inhibitors

S. Divya, N. Bhavya, K. Pavan Kumar, K. Srujana Keerthi and M.D. Dhanaraju

Department of Pharmacology, GIET School of Pharmacy, NH-5, Chaitanya nagar, Rajahmundry andhra Pradesh, India

Abstract: Angiotensin converting enzyme (ACE) inhibition is a well established principle in the treatment of hypertension and numerous large scale clinical studies have clearly demonstrated the beneficial effects of inhibiting the Renin Angiotensin Aldosterone System [RAAS] in hypertension. The clinical success of ACE inhibitors encouraged attempts to inhibit other key enzymes in the regulation of vascular tone, such as the neutral endopeptidase (NEP). Similar to ACE, NEP is an endothelial cell surface zinc metalloproteinase which is involved in the degradation of several regulatory peptides including the natriuretic peptides (Atrial natriuretic peptide [ANP], Brain natriuretic peptide [BNP], C-type natriuretic peptide [CNP] and Dendroaspis natriuretic peptide [DNP] and augments vasodilatation. By inhibiting the RAS and potentiating the natriuretic peptide system at the same time, combined NEP/ACE inhibitors so called ‘Vasopeptidase inhibitors’, reduce vasoconstriction and enhance vasodilatation and in turn decrease peripheral vascular resistance and Blood Pressure.

Key words: Angiotensin converting enzyme • Neutral endopeptidase • Natriuretic peptides • Urodilatin and Renin angiotensin aldosterone system

INTRODUCTION

The RAAS plays a vital role in cardiovascular regulation both as a circulating and paracrine local vascular system [1]. ACE catalyses the conversion of Angiotensin I into Angiotensin II, a potent vasoconstrictor agent playing a central role in the pathogenesis of hypertension [2]. Angiotensin II increases production of endothelin-1, superoxide anion and PAI-1, an inhibitor of fibrinolysis, both of which promote vasoconstriction and thrombosis [3, 4]. The beneficial effect of ACE inhibition has been documented in many trials for the treatment of hypertension [5, 6]. ACE inhibitors not only prevent the formation of a potent vasoconstrictor with proliferative properties, but also increase the local concentration of bradykinin and in turn the production of Nitrous Oxide [NO] [7] and prostacyclin, which may contribute to the vascular protective effects of the ACE inhibitors by improving local blood flow and preventing platelet activation. Therefore the mechanism involves decrease in the formation of Ang-II, reduction of vasoconstriction through increased bioavailability of bradykinin, decreased proliferation of smooth muscle cells, reduced release of superoxide anion, inhibition of release of Endothelin-1 [ET-1] [8-10]. Similarly Vasopeptidase inhibitors inhibits both ACE and NEP and beneficial as Antihypertensive agents.

Neutral Endopeptidase (NEP): NEP located primarily in the kidneys which functions to degrade the natriuretic peptides, these peptides behave as antagonists to RAS causing vasodilation. Competitive inhibitors of NEP were used to maintain the high levels of natriuretic peptides (ANP, BNP, CNP and DNP), bradykinin, adrenomedullin and thus lowers blood pressure.

NEP-Inhibitors: They decrease the degradation of natriuretic peptides and increase their endogenous level [11].They have proven to be beneficial for CHF. Treatment with NEP inhibitors improved cardiac output index [12], decreased left atrial and arterial pressure [13], decreased pulmonary capillary wedge pressure and induced potent natriuresis [14]. Decrease the degradation Ang-II which may antagonize the effects of NP’s [15]. They show more potent antihypertensive effect than ACE inhibitors for its independence of plasma levels of rennin [16].
Natriuretic Peptides: NP’s are group of structurally related but genetically distinct peptides. NP’s play a key role in antagonizing the actions of RAAS thus promoting vasodilation and natriuresis. There are several types of NP’s which are both exogenous and endogenous may be a chimerical NP’s or venom derived NP’s.

Chimeric NP’s: It is obtained from the administration of desired properties of NP’s in to one molecule, E.g.: Vasonatrin peptide obtained from 22 amino acid sequence of CNP and 5 amino acid C-terminal part of ANP [18.52]. E.g.: CD-NP obtained from ring structure of CNP and the 15 amino acid sequence of N-terminal sequence of DNP [19, 53].

Receptors of NP: NP’s exert their effects through interaction with high affinity receptors such as NPR-A, NPR-B, NPR-C. ANP, BNP and urodilatin acts through NPR-A receptors. NPR-A activates guanylyl cyclase which leads to the production of C-GMP, mediates vasodilation, natriuresis, positive lusitropism. CNP acts through NPR-B receptors, activates guanylyl cyclase leads to production of C-GMP mediates vasodilation. NPR-A receptor is the most abundant type in large blood vessels but there are also some B receptors. NPR-B receptors are predominant in brain. Both A & B receptors are present in the adrenal glands and kidneys. In both A and B receptors the extracellular portion is linked to the intracellular portion by a single membrane spanning segment. The intracellular portion contains a kinase-like domain, followed by the guanylyl cyclase catalytic domain. Binding of the natriuretic peptides to their receptors activates guanylyl cyclase, leading to an elevation in intracellular CGMP causes vasodilation. NP’s secretion is modulated by Endothelin-1, Angiotensin-II, Estrogen, Interleukin I. clearance of NP’s can be done by different ways which includes, NP’s by NEP, produced and excreted by kidneys, BNP cleaved by Meprin-A [20] and dipeptidyl peptidase-4 [21]. CGMP degraded by phosphodiesterases such as PDE-5, inhibitor Sildenafil. The discussed four NP’s are cleared by the help of clearance receptors NPR-C and also undergo lysosomal degradation.

Production and Release of the Natriuretic Peptides:
The primary stimulus for the secretion and release of ANP and BNP is an increase in atrial stretch or pressure of some hormones and neurotransmitters such as Endothelin and Ang-II may also play a role. Production and release of CNP is mainly enhanced by cytokines, including transforming growth factor-β, tumor necrosis factor, IL-1β, IL-1α, basic fibroblast growth factors and lipopolysaccharides.

Table 1: Different types of Natriuretic Peptides [17]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Natriuretic peptides</th>
<th>Isolation/production</th>
<th>Physiologic effects on CVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>ANP (atrial natriuretic peptide)</td>
<td>Mainly from atrial myocardium</td>
<td>Controls excess salt and water retention, vasodilatation, increase GFR, sodium excretion, inhibition of RAAS and plasma endothelin release.</td>
</tr>
<tr>
<td>2.</td>
<td>BNP (Brain natriuretic peptide)</td>
<td>Mainly from ventricles of Brain</td>
<td>Vasodilation, sodium excretion, controls excess salt and water retention.</td>
</tr>
<tr>
<td>3.</td>
<td>CNP (C-type natriuretic peptide)</td>
<td>Produced in endothelial cells</td>
<td>Lacks significant natriuretic function but potent vasodilatation is produced.</td>
</tr>
<tr>
<td>4.</td>
<td>DNP (Dendroarapis natriuretic peptide)</td>
<td>Isolated from venom of green mamba</td>
<td>Renal &amp; cardiovascular functions in mamba.</td>
</tr>
</tbody>
</table>
ANP: It is mainly produced from the atrial myocardium. ANP precursor peptide resides on chromosome ip 36.2. Its m-RNA encodes a precursor peptide pro-ANP, a 126 aminoacid peptide. Cleavage of ANP releases mature 28 aminoacid ANP and 98 aminoacid terminal fragments. ANP is a potent factor controlling excess salt and water retention and high BP [22] which is mediated by the inhibition RAAS as well as plasma endothelin release [23]. It also increases vascular permeability to induce a fluid shift from intravascular to the interstitial [24]. Sustained low dose infusion of ANP induces the reduction of PVR and BP. The endogenous ANP also plays a role in the control of renal sodium excretion and volume expansion [25]. Nakao et al. [26] studied the pharmacokinetics of synthetic α-human ANP using i.v bolus injection. The disappearance of α-hANP with fast and slow half-times was of 1.7 min and 13.3 min, respectively. Weidmann et al [27] showed that, the i.v infusion of synthetic α-hANP lowered systemic blood pressure, increased glomerular filtration rate in healthy men. i.v infusion of ANP decreases pulmonary capillary wedge pressure renal response in heart failure patient when compared to normal. Because, the down regulation of NP receptors in kidneys causes, reduced production or increased degradation of CGMP, increased activity of NEP, increased renal sympathetic activity. More recently the efficacy and safety for carperitide (human recombinant ANP) was approved in Japan in 1995.

BNP: It is mainly produced in the ventricle of brain [28]. The human BNP precursor peptide resides on chromosome ip 36.2. Human pro-BNP contains 108 aminoacids, processing of BNP releases a mature 32-aminoacid molecule and an amino terminal fragment [29]. BNP exerts similar natriuretic and vasodilation functions as ANP [30], except that BNP doesn’t increase GFR in humans [31]. Distribution half life is of 2 min and mean terminal elimination half life of recombinant BNP is of 18 min [32]. The time to steady state level is less than 90 min and the mean volume of distribution is 0.191 kg⁻¹. Nesiritide a purified preparation of human BNP, is manufactured from E.coli using recombinant DNA technology. Recombinant BNP exhibits similar physiologic actions as endogenous BNP. Ventricular stretch is a very important stimulus for BNP production.

CNP: It is mainly produced in endothelial cells [33]. The encoding gene of human CNP precursor peptide resides on chromosome 2, which encodes a CNP precursor of 126-aminoacid [34]. The precursor undergoes subsequent processing and generates 22 and 53-aminoacid peptides [35]. The 22-form is the major form of CNP as it is more potent and more widely expressed than 53-form. In contrast to ANP and BNP, CNP lacks significant natriuretic function [36]. The potent vasodilator effect of CNP was confirmed both in animal models and in humans. Both ANP and BNP stimulate the production of CNP in endothelial cells [38].

DNP: It has been isolated from the venom of Dendroaspis augusticeps (the green mamba snake). It is a 38-amino acid peptide a strong homolog with ANP. In addition, it has a unique 15-amino acid extension in the C-terminus [39]. DNP exhibits functional features that are characteristic of NP’s. In the human myocardium, singh et al. demonstrated the selectivity of DNP using radioiodinated analog of DNP [40]. DNP- like immune activity has been detected in isolated arteries and veins from humans [41]. It has been shown to exert vasorelaxant effects on canine coronary arteries [42]. In vivo cardiovascular studies of synthetic DNP were evaluated in a canine study by Lainchbury et al [43]. The renal actions of i.v infusion of synthetic DNP were assessed by Lisy et al [44]. NEP inhibition did not augment the renal actions, suggesting that DNP might be resistant to degradation by NEP [45].

Urodilatin: Cartens et al. studied the pharmacokinetics and renal pharmacodynamics of urodilatin. It was administered as a 90 min infusion. It possesses a large volume of distribution 43.7 l, a high total body clearance (5.358 l/min⁻¹) and a short plasma half life of 5.57 min [46]. Infusion of urodilatin in healthy man exerted natriuretic and diuretic effects with lowering of mean blood pressure. Urodilatin in the dose between 5ng kg⁻¹ min⁻¹ and 10ng kg⁻¹ min⁻¹ did not change mean arterial pressure but decrease stroke volume and cardiac output. In addition dose dependent increase in urinary cGMP and Na⁺ excretion were observed, with URO being more potent than ANP [47]. There was an increase in GFR followed by the administration of URO 50µg and 100µg. There were no changes in effective RBF, plasma rennin, aldosterone/catecholamines. The safety and efficacy of SIRIUS-11 has been evaluated by intravenous infusion.
Fig. 1: Role of NP’s Natriuretic Peptides on Cardiac Failuregressive LV dysfunction


The above genetically distinct hormones are produced as prohormones and cleaved by a transmembrane protein named corin.

**List of Drugs:** NEP inhibitors include candoxatril, thiorphan, phosphoramidon and selective NEP inhibitor is SQ-28603 which only inhibits neutral endopeptidase. Vasopeptidase inhibitors include, omapatrilat, sampatrilat, fasidotril, glycopatrilat, candotril, alatripatrilat, xandoxatril, AVE 7688, CGS 35601 which inhibits both ACE and NEP. Recombinant human BNP is nesiritide safe and effective in patients with CHF. Natriuretic peptide mimetic (chimera of ANP and CNP) is vasonatrin, it has vasodilator effect of CNP, natriuretic effect of ANP and
arterial vasodilation effect. ANP mutant from rat is RANP (REA 18), it has higher affinity to NPR-A and lower affinity to NPR-C, displayed longer half life, more potent natriuretic and vasorelaxation effect than native ANP.

**Therapeutic Uses**

**Hypertension:** Hypertension is an increase in peripheral vascular resistance, which in turn increases the vascular tone by the release of constricting factors. Though the ACE inhibitors are useful in treatment of hypertension, about 50% of patients need additional therapy [61]. Most important benefits of vasopeptidase inhibitors are their capability to reduce blood pressure independently of volume or rennin status. In contrast, ACE inhibitors are predominantly effective in patients with rennin dependent hypertension and NEP inhibitors work effective in patients with low rennin, volume dependent hypertension.

**ADHF:** Natriuretic peptides help in suppression of RAAS and SNS. So these include the decrease in systemic vasodilation with decreased after load so the right arterial pulmonary artery and pulmonary capillary wedge pressure tends to decrease so it results to increased cardiac index and so these are used in therapy of ADHF (acute decompensated heart failure) [11, 12, 62, 63].

**CHF:** Congestive heart failure in acute or chronic form is characterized progressive left ventricular systolic and/or diastolic dysfunction. Acute administration of BNP in CHF enhances the diastolic function, which was superior to the effect of ANP as it is important therapeutically because specific treatment of diastolic HF is lacking [64]. Emergence of renal resistance to NP’s may require a specific multidrug therapy. In contrast with small molecules used to alter systems involved in pathogenesis of CHF, such as RAAS and SNS, the utility of NP’s gives several advantages and challenges (Figure: 1). Subcutaneous administration of NP’s led to successful results without developing tolerance to BNP [22, 39, 40].

**Clinical Trails:** ASCEND-HF- acute study of clinical effectiveness of Nesiritide in decompensated heart failure. FUSION- follows up serial infusions of nesiritide in advanced heart failure. MONICA- monitoring trends and determinants in cardiovascular diseases [65]. Omapatrilat reduces the risk of death and hospitalization in chronic heart failure and is slightly more effective than enalapril but the future of omapatrilat is determined by its unfavourable side effects, angioedema in patients [66]. In clinical studies, side effects were comparable with those of ACE inhibitors: cough and flush in 573 patients in the inhibition of metalloproteinase in a randomized exercise and symptoms in heart failure (IMPRESS) trial were reported [67]. ADHERE - Acute Decompensated Heart Failure National Registry, NAPA- Nesiritide Administered Peri-Anaesthesia in patients undergoing cardiac surgery. OVERTURE- omapatrilat versus Enalapril Randomized Trail of Utility in reducing events, designed to compare the efficacy of Omapatrilat with that of enalapril, in patients with heart failure. Study indicates Omapatrilat group had a 9% lower risk of cardiovascular death or hospitalization (p = 0.024) and a 6% lower risk of death (p=0.339). The OCTAVE (Omapatrilat Cardiovascular treatment Assessment versus Enalapril) trial, designed especially to evaluate the risk of adverse effects on omapatrilat treatment in low doses. Study indicates that, in the treatment of hypertension Omapatrilat indeed is safe and documented adverse effects do not exceed those of other commonly used antihypertensive compounds like Enalapril. In normotensives, oral administration of Omapatrilat leads to long-lasting (>24 hours) and dose-dependent ACE inhibition and increases in urinary ANP levels. In a randomized double blind, placebo-controlled study on 36 normotensives, Omapatrilat potently lowered blood pressure in a dose dependent manner. The peak effect was registered in the first 3 to 8 hrs and was sustained for 24 hrs, comparison with other antihypertensive agents, such as lisinopril, losartan and amlopidine revealed more pronounced antihypertensive effects of Omapatrilat, particularly in the systolic range. The pronounced effects of Omapatrilat on systolic pressure suggest that large artery compliance and structure may be favourably affected. In cardiomyopathic hamsters with CHF, short term administration of Omapatrilat reduced left ventricular systolic and end diastolic pressure. These changes were associated with a 40% increase in cardiac output and a 47% decrease in peripheral vascular resistance and were significantly greater after administration of omapatrilat than with SQ - 28603 (a selective NEP inhibitor) or the ACE inhibitor Enalapril. In an experimental Canine model of CHF, Omapatrilat was superior to ACE inhibition alone in inducing an increase in sodium excretion and GFR, in addition to a greater decrease in pulmonary capillary wedge pressure.
CONCLUSION

In all preclinical and clinical trials completed so far, vasopeptidase inhibition has proven highly effective in various forms of hypertension. But due to their short half-life when given intravenously and inactive given orally, novel cardiovascular drugs will have to come up with an excellent profile of beneficial effects and minimized side effects. Vasopeptidase inhibition beneficial in diabetes, endothelial dysfunction and renal failure, are common conditions among cardiovascular patients. In addition several trials like OVERTURE, OPERA, IMPRESS, OCTAVE studies are going on to estimate the safety and efficacy of vasopeptidase inhibitors.

REFERENCES


