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# Vasopeptidase inhibitors—concepts and evidence

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## Introduction

Structural, humoral and neuronal factors are involved in cardiovascular regulation. The renin–angiotensin–aldosterone system (RAAS) plays a central role in cardiovascular regulation as both a circulating hormone and a paracrine mediator. The endothelium is a source of paracrine mediators such as nitric oxide (NO), endothelial-derived hyperpolarizing factor (EDHF) and endothelin (Figure 1). These circulating and local regulatory systems exhibit complex synergisms and interactions; the sympathetic nervous system stimulates secretion of rennin and angiotensin II which, centrally and at the presynaptic level, increase sympathetic nerve activity and enhance endothelin and vasopressin production. Atrial natriuretic peptides on the other hand counteract the RAAS and endothelin. Endothelial substances act primarily locally and exhibit vasoconstrictor, vasodilating, and mitogenic effects. All these regulatory systems are responsible for proper circulatory homeostasis and for structural vascular and myocardial regulation.

Although neurohumoral systems are essential in vascular homeostasis, they become maladaptive in disease states such as hypertension, coronary disease, and heart failure. The clinical success of blocking the renin–angiotensin–aldosterone system by angiotensin-converting enzyme inhibitors has led to efforts to block other humoral systems as well. Neutral endopeptidase (NEP) is an endothelial cell surface zinc metallopeptidase with similar structure and catalytic site. NEP is the major enzymatic pathway of degradation of natriuretic peptides and a secondary enzymatic pathway for degradation of kinins.

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## Natriuretic peptides

The family of natriuretic peptides consists of three isoforms, namely atrial (ANP), brain (BNP), and C-type natriuretic peptide (CNP). ANP infusion reduces blood pressure while increasing urine volume, urinary excretion of sodium, cyclic GMP, inhibits renin and aldosterone secretion [1], and increases the hypotensive effect of BNP. Moreover, ANP inhibits endothelin production and proliferation of vascular smooth cells and myocardial hypertrophy, and ANP has been shown to have significant sympatholytic effects as well. Because of its biological effect (an antagonist to angiotensin II), ANP is an endogenous inhibitor of the RAAS. ANP production in the myocardium is induced by increased atrial pressure, water retention, increased sodium intake and decreased left ventricular function.

Natriuretic peptide levels are elevated in hypertensive patients, in left ventricular hypertrophy and early CHF [2]. Although in early CHF augmented levels of natriuretic peptides may prevent water and sodium retention, a relative decrease of ANP production and an escape phenomenon of the RAAS, leading to increased water and natrium retention, occur later in advanced CHF.

Circulating ANP is quickly metabolized and inactivated by specific enzymes, neutral endopeptidases in particular (Figure 1). The short half-life of ANP, as well as the fact that the peptide is both difficult to administer and expensive, limits the option of an exogenous application of the peptide as a possible therapeutic strategy. Therefore, pharmacological inhibition of the metabolism of natriuretic peptides is an attractive alternative therapeutic target.

## Neutral endopeptidases

NEP is an endothelial, membrane-bound zinc metallopeptidase that cleaves endogenous peptides at the amino side of hydrophilic residues. It has a catalytic unit similar to ACE for degradation of a number of endogenous vasodilator peptides, including ANP, BNP, CNP, substance P, and bradykinin as well as vasoconstrictor peptides, including endothelin-1 and angiotensin II. NEP is widely distributed in endothelial cells, vascular smooth-muscle cells, cardiac myocytes, and renal epithelial cells as well as in fibroblasts.

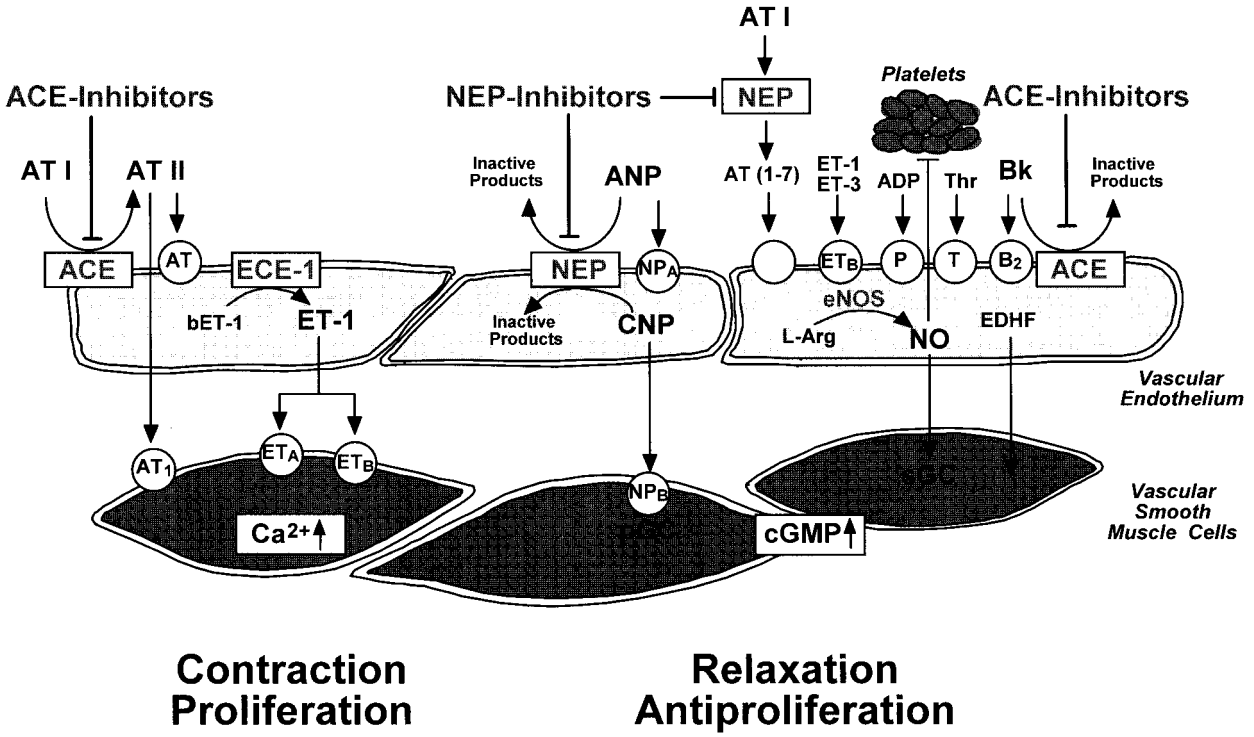


**Fig. 1.** The synergistic effects resulting from combined ACE and NEP inhibition, are due to similar mechanism, leading to the blockade of angiotensin (AT) synthesis and concomitant potentiation of the effects of natriuretic peptides and bradykinin, leading to vasodilatation, natriuresis, and improvement in myocardial function.

Chronic treatment with NEP inhibitors augments the effects of ANP and lowers blood pressure in hypertension. However, the antihypertensive effects may be offset by an increased activity of the RAAS and sympathetic nervous system and/or down-regulation of ANP receptors.

As NEP is also involved in the degradation of vasoconstrictors, e.g. endothelin-1, this explains why pure NEP inhibitors decrease forearm blood flow [3] and fail to lower blood pressure. The blood-pressure response to selective endopeptidase inhibition in hypertension depends on the relative effects on vasodilator (including ANP) and vasoconstrictor (including the RAAS and sympathetic) systems. Furthermore NEP is involved in the metabolism of kinins. Under physiological conditions NEP accounts in most tissues for only a small portion of the metabolism of kinins, but in human cardiac tissue NEP accounts for nearly half of the metabolism of bradykinin. However, NEP becomes a major pathway for the breakdown of bradykinin when ACE is inhibited.

## Combined ACE and NEP inhibitors

In many cardiovascular and renal diseases, an array of regulatory mechanisms is involved, making drugs with multiple modes of action promising. As ACE inhibition blocks the action of angiotensin II, thus enhancing the effects of ANP, and NEP inhibitors lower blood pressure more effectively in salt- and volume-dependent than in renin-dependent forms of hypertension [4], the combination of ACE and NEP inhibition may be particularly useful in cardiorenal diseases. Indeed, the haemodynamic and renal effect achieved by simultaneous inhibition of ACE and NEP is more pronounced than after selective inhibition.

By convention, agents that simultaneously inhibit two of the three important cardiovascular enzymes, ACE, NEP, or ECE, are termed vasopeptidase inhibitors.

## Vasopeptidase inhibitors and hypertension

Omapatrilat—a potent oral dual NEP/ACE inhibitor—induces long-lasting hypotensive effects in low-, and high-renin models of hypertension greater than those elicited by selective inhibition of either enzyme along. Thus, combined NEP/ACE inhibition may be an effective and broad-spectrum antihypertensive principle [5].

In salt-induced hypertension, omapatrilat was more efficient in reversing structural changes and endothelial dysfunction than captopril. In the aorta of the same model, both omapatrilat and captopril increased eNOS expression to a similar degree, while only

omapatrilat increased ANF levels and normalized endothelium-dependent relaxations to acetylcholine [6].

In a clinical study in 36 normotensive subjects, omapatrilat potently lowered blood pressure in a dose-dependent manner. The peak effect was registered in the first 3–8 h and was sustained for 24 h. In human hypertension, omapatrilat induced greater antihypertensive effects in comparison with lisinopril, losartan, and amlodipine [7].

## Vasopeptidase inhibitors and renal function

Omapatrilat and its metabolites do not significantly accumulate in patients with renal insufficiency. Furthermore, haemodialysis does not contribute to the clearance of omapatrilat [8].

In experimental heart failure omapatrilat increased urinary sodium excretion. It is of note that effective renal plasma flow and glomerular filtration rate increased or were stable in mild and severe CHF after both acute and repeated dosing [9]. In experimental two-kidney, one clip (2K1C) hypertension omapatrilat has been shown to reduce glomerulosclerosis more effectively than enalapril, and prevent vascular hypertrophy [10]. In severe salt-induced hypertension omapatrilat prevented vascular hypertrophy and restored renovascular endothelial function, but had only a modest effect on glomerular injury [6].

## Vasopeptidase inhibitors and congestive heart failure

In cardiomyopathic hamsters with CHF, acute administration of omapatrilat improved haemodynamics and prolonged survival in comparison with ACE inhibitors alone [11].

In the IMPRESS (Inhibition of MetalloProteinase in a Randomized Exercise and Symptoms Study in Heart Failure) trial, 573 patients with CHF (63% NYHA II and 37% NYHA III/IV) were randomized to receive either omapatrilat (40 mg daily) or lisinopril (20 mg daily) [12]. Omapatrilat ameliorated clinical status and reduced the combined morbidity/mortality end-point to a greater extent than lisinopril. Both drugs were well tolerated, but serious adverse events and marked elevations of serum creatinine were less frequent with omapatrilat.

## Vasopeptidase inhibitors and angioedema

Angioedema is a serious and potentially fatal complication in patients treated with ACE inhibitors, which is relatively rare in the general population but more common amongst black/Afro-Caribbean patients, with an incidence of 0.1–0.5%. The mechanism remains unclear. Bradykinin and its metabolite des-arg$^9$–bradykinin have been implicated in ACE-induced angioedema. Hence, vasopeptidase inhibitors acting simultaneously on two enzymes that inactivate bradykinin, i.e. ACE and NEP, may potentially increase the risk of angioedema. The OCTAVE (Omapatrilat Cardiovascular Treatment Assessment *vs* Enalapril) trial investigates in 25 000 untreated or poorly controlled hypertensives whether force titration of omapatrilat from 10 mg to 20 mg (with elective up-titration to 80 mg) is or is not associated with a higher incidence of angioedema than enalapril.

## Conclusion

The encouraging experimental and clinical results of vasopeptidase inhibitors have set the stage for morbidity/mortality clinical trials. Some are already under way (OVERTURE trial). They will provide the answer to whether combined ACE/NEP inhibitors offer a benefit for our patients with cardiovascular and renal disease.

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