Dual Endothelin-Converting Enzyme/Neutral Endopeptidase Inhibition

A Novel Treatment for Renovascular Hypertension Beyond Blood Pressure Lowering?

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The endothelin (ET) family consists of three 21-amino acid peptides (ET-1, ET-2, and ET-3) with powerful vasoconstrictor and pressor properties. Of the 3 peptides, ET-1 is the major vascular isoform and of most importance in the cardiovascular system. The gene product is the 212-amino acid preproET-1. This is cleaved to Big-ET-1, after which an ET-converting enzyme (ECE), of which there are several isoforms, catalyzes the generation of the biologically active ET-1 and a C-terminal fragment.

ET-1 has 2 distinct binding sites, the ETA and the ETB receptors. ET receptors are expressed by a wide variety of cells and tissues. Within the vasculature, ETA and ETB receptors located on vascular smooth muscle cells mediate the vasoconstrictor effects of ET-1. ETB receptors are also found on vascular endothelial cells, where their activation results in vasodilation mediated mainly by NO. In addition, ETB receptors have a major role in clearance of circulating ET-1.

The ET system is upregulated in a number of cardiovascular diseases, and its antagonism has shown promising therapeutic potential. Similar to angiotensin II, there are 2 pharmacological mechanisms for inhibiting the actions of ET-1, either at the point of its binding to its cognate receptors or by blocking its generation. Much of the work on ET blocking strategies has focused on the first of these. The last 10 years have seen the clinical development of a large number of selective ETA receptor and mixed ETAB receptor antagonists (see Table in Reference). The major clinical problem with these agents has been the adverse effect of fluid retention, which, although stopping some clinical trials, has been shown to be manageable in others. ECE inhibition provides another potentially exciting method of blocking the ET system. By blocking ET-1 generation, these agents would act in a similar manner to mixed ETAB receptor antagonists, without affecting ETB receptor–mediated ET-1 clearance. However, there are potential problems with blocking ECE. First, it remains uncertain to what extent the ET system will be blocked. Not only do there exist a number of non-ECE ET-1 generating enzymes, but also the extent to which the different ECE isoforms would be blocked is unclear. Although a reduction in ET-1 synthesis may be desirable, other isoforms, such as ET-3,5 may have physiological functions that should not be compromised. Second, similar to angiotensin-converting enzyme inhibition, there may be the phenomenon of escape from ECE inhibition. Finally, there is a potential risk of angioedema with these drugs, although this may only occur when ECE and angiotensin-converting enzyme inhibition are combined.

Neutral endopeptidase (NEP) catalyzes the degradation of a number of endogenous vasodilator peptides, including atrial natriuretic peptide. Atrial natriuretic peptide has potent natriuretic and vasodilator effects and also inhibits activity of the renin-angiotensin system (RAS) by reducing both renin and aldosterone release. Therefore, NEP inhibition is an attractive therapeutic approach in cardiovascular diseases associated with hypertension and fluid overload. However, although NEP inhibitors do increase natriuresis, their ability to lower BP has been less impressive. This is probably because of the fact that NEP also inhibits the degradation of vasoconstrictor peptides, such as angiotensin II and ET-1, with studies showing that an increase in ET-1-mediated vasoconstriction11 is the likely explanation for NEP inhibition not lowering BP. Thus, the combination of ECE and NEP inhibition appears logical (see Figure). This would counterbalance both the increased concentration of ET-1 seen with NEP inhibition and provide a mechanism to increase diuresis and natriuresis and so reduce the adverse effect of fluid retention seen with ET system blockade.

In the present issue of Hypertension, Kalk et al12 describe a series of in vivo experiments using the dual ECE/NEP inhibitor SLV388 in the well-established 2-kidney, 1-clip (2K1C) Goldblatt model of hypertension. This is a form of secondary hypertension that is similar in many ways to human renovascular hypertension and is highly dependent on the increased activity of the RAS. In both low and high doses of the dual inhibitor, with these doses corroborated for significant ECE and NEP inhibition in vitro and in vivo, the authors show a complete abrogation of the interstitial fibrosis seen in the hearts of 2K1C rats. Similar beneficial and preventative effects of SLV88 were seen on the increased
perivascular fibrosis, elevated media:lumen ratio of the cardiac arteries, and increased cardiomyocyte diameter, all features of the Goldblatt model. Losartan, a noncompetitive antagonist at the angiotensin II type 1 receptor, showed similar effects to SLV88. Of most interest is the fact that, whereas losartan reduced BP significantly in the 2K1C model (by up to \( \approx 45\) mm Hg), SLV88 had no discernible effect on BP, suggesting that the cardioprotective effects of SLV88 appear to be BP independent. With regard to a potential mechanism for the effects seen, the authors show that, in untreated 2K1C rats, there is a marked upregulation of cardiac TGF-\( \beta \) expression compared with sham-operated animals. This is completely prevented by both SLV88 and losartan.

The authors concentrate on the effects of ECE/NEP inhibition on the cardiac pathology of the Goldblatt model. However, this is a model of renovascular hypertension and is associated with specific changes in renal hemodynamics and intrarenal RAS. Exploring the effects of ECE/NEP inhibition on these aspects, and comparing them with standard RAS blockade alone, would be of interest and clinical relevance, given that chronic kidney disease is an important independent risk factor for cardiovascular disease. Indeed, a study in a rat model of diabetic nephropathy has suggested that dual ECE/NEP inhibition is as good as angiotensin-converting enzyme inhibition in reducing proteinuria. In this study, ECE/NEP and angiotensin-converting enzyme inhibition both also reduced renal interstitial matrix content, as seen in the heart in the current study.

Although Kalk et al.\(^{12} \) show that the doses of ECE inhibition used are sufficient to adequately block the increase in systolic BP in response to big ET-1, they do not show baseline plasma ET-1 concentrations or ET-1 message in cardiac tissue, or how these change with ECE/NEP and RAS inhibition. This would be noteworthy, because previous data in a hypertensive rat model suggest that plasma ET-1 levels correlate with cardiac sizes and perivascular fibrosis. Furthermore, in this model of left ventricular hypertrophy and congestive heart failure, the benefits of dual ECE/NEP inhibition are thought in part to relate to a greater reduction in plasma ET-1 compared with RAS blockade alone.\(^ {15} \)

The significant benefits of ECE/NEP inhibition in the absence of a BP response are very interesting. This likely relates to the nature of the 2K1C model, because other animal models treated with ECE/NEP inhibition show a fall in BP similar to that achieved with RAS inhibition.\(^ {14,15} \) The Goldblatt model is one of RAS overactivity, and so to reduce BP effectively a greater degree of RAS inhibition is probably required than that achievable with ECE/NEP inhibition alone. It does leave us with the intriguing question: what is the mechanism for the cardioprotection seen with SLV388 if not BP lowering? Although the reduction in transforming growth factor-\( \beta \) expression is unsurprising, given that this is a common downstream component of many signaling pathways, it does provide a basis for further exploratory mechanistic studies.

Dual ECE/NEP inhibitors have been slow to emerge as therapeutic agents probably because of the difficulty in synthesizing compounds with a sufficiently high degree of inhibition at both enzymes. The current data are interesting and provide a platform for future preclinical and clinical studies exploring the concept of combined ECE/NEP inhibition as a novel treatment for renovascular hypertension and its downstream effects or as an alternative to ET receptor antagonists for their growing indications.

**Disclosures**

None.

**References**


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