Endothelin Receptor Antagonists
Promising New Agents in the Management of Cardiovascular Disorders

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Abstract
Since its discovery in 1988, endothelin (ET) has been widely implicated in the pathophysiology of cardiovascular disease. ET antagonists have favourable effects in experimental models of these conditions and have proved useful in elucidating the role of the ET system. Orally acting ET antagonists appear very promising in clinical trials, particularly in patients with chronic heart failure and hypertension, but more information on the roles of the ET receptor subtypes in health and disease is required so that an informed choice can be made between the use of endothelin-A (ET-A) receptor-selective and nonselective receptor antagonists.

The endothelins (ET) are a family of 21 amino acid peptides with powerful vasoconstrictor and pressor properties that were first described by Yanagisawa et al. in 1988.[1] Three different isopeptides, endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3), have so far been identified, each with distinct genes and tissue distributions.[1-3] Of the 3 peptides, ET-1 is the major endothelial isoform and is therefore likely to be the most important in the regulation of cardiovascular function. Therefore, this article, focuses primarily on ET-1. Its main site of production is the vascular endothelial cell but it is also produced by other cell types, including renal tubular and mesangial cells, vascular smooth muscle cells and epicardial cells.[4-6] In addition to its vasoconstrictor properties, ET-1 functions as a mitogen, modulates other hormone systems and influences ion and fluid transport in the gut and kidney.[7,8]

Regulation of the production of ET-1 is thought to be at the level of gene transcription. Enhanced gene transcription occurs in response to a wide range of stimuli including other vasoactive hormones [such as angiotensin II, adrenaline (epinephrine) and vasopressin], cytokines (such as interleukin-1 and endotoxin), and hypoxia, glucose and oxidised low density lipoprotein (LDL). In contrast, prostacyclin, nitric oxide (NO) and the natriuretic peptides all inhibit transcription of endothelin genes. The gene product is prepro-ET-1, a protein with 212 amino acids which is cleaved in stages to yield the largely inactive big ET-1, a 38-amino-acid precursor peptide. Endothelin converting enzyme (ECE), a metalloproteinase, then splits big ET-1 into the active mediator, ET-1, and its C terminal fragment[9] (fig. 1).

Two ET receptors have been identified and cloned: endothelin-A (ET-A) receptors have a higher affinity for ET-1 than either ET-2 or ET-3, whereas endothelin-B (ET-B) receptors have equal affinity for the 3 ET peptides.[10-12] Within the circulation, ET-A receptors are found on vascular smooth muscle cells and their activation results in vasoconstriction. ET-B receptors are also found on vascular smooth muscle cells, where they mediate vasoconstriction. However, ET-B receptors are more abundant on the vascular endothelium where their
activation results in vasodilatation mediated by NO and prostacyclin. In the human kidney, ET-A receptors are localised to vascular smooth muscle, notably in the glomeruli, vasa recta and arcuate arteries. ET-B receptors are more numerous (ET-B to ET-A ratio 2 : 1) and more widespread with a high concentration in the collecting system.[13] The distribution of these receptors within the kidney suggests a vasoactive role for ET-A receptors and a role in sodium and water handling for ET-B receptors.

Signal transduction is complex and reviewed elsewhere.[9] ET-1 is removed in the renal, splanchnic and pulmonary circulations, probably by ET-B receptor binding and internalisation and also enzymatic degradation by neutral endopeptidases.[14]

1. Endothelin Receptor Antagonists

Compounds that block the ET system have been used to define the role of the endogenous ET system and confirm its importance in cardiovascular function and dysfunction. Attention is now focusing increasingly on drugs that may have a role in clinical medicine. Though ECE inhibitors and monoclonal antibodies have been used experimentally,