

Endothelins

Overview

The endothelin family of peptides consists of highly potent endogenous vasoconstrictor agents first isolated from endothelial cell supernatant. Of the 3 isoforms (ET-1, ET-2, ET-3), endothelin-1 is the major isoform and plays an important role for regulation of vascular function. Two endothelin receptor subtypes have so far been cloned in mammalian species: ET(A) and ET(B). Both receptor subtypes are found on smooth muscle cell. ET(A) receptor mediates the proliferative and vasoconstrictive effect and ET(B) mediates vasodilatation through release of nitric oxide and prostacyclin. A unique membrane-bound metalloprotease, endothelin-converting enzyme cleaves both intra- and extracellular big ETs to the 21-amino-acid bioactive form (ET-1, ET-2 and ET-3), and is structurally related to neutral endopeptidase 24.11.

Endogenous endothelin peptides and their receptors are differentially distributed throughout the many smooth muscle tissues including blood vessels, uterus, bladder and intestine. Through this widespread distribution and localization, they exert biological functions in regulating vascular tone and causing mitogenesis. ETs and their receptor subtypes are also present in various endocrine organs. It appears to act as a modulator of secretion of prolactin, gonadotropins GH and TSH. Endothelin may also be the disease marker or an etiologic factor in ischemic heart disease, atherosclerosis, congestive heart failure, renal failure, systemic hypertension, pulmonary hypertension, cerebral vasospasm.

To date, the investigation of the endothelin system has been greatly advanced through significant advances in the development of potent and selective ET receptor antagonists. Among these, BQ-123, a cyclic pentapeptide possessing three D-amino acids from a fermentation broth of *Streptomyces*, is the most widely studied ET(A) receptor antagonist. Other peptide compounds, such as BQ-788, a pseudotriptide with high affinity for ET(B) receptor, FR-139317, a modified tripeptide with potent ET(A) antagonist function, and RES-701, a highly selective ET(B) antagonist, also show very interesting ET receptor antagonist properties. Several nonpeptide ET receptor antagonists were also identified and developed. Bosentan (Ro-47-0203), a nonselective ET(A)/ET(B) antagonist, is the most widely studied nonpeptide compound. These pharmacological agents have proven to be essential tools for understanding the biological significance of the ET system, as well as providing the significant therapeutic potential for treatment of a variety of cardiovascular diseases.

The fascination of this field of research is underscored by a great number of publications, review articles published in the scientific literature, as well as numerous symposia held on the subject at major research centers.

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