

Endothelin Receptors

Key References

- Bagnato, A., Therapies for cancer targeting endothelin receptors., *Drugs Future*, **28**, 983-989 (2003).
- Benigni, A. and Remuzzi, G., Endothelin antagonists., *Lancet*, **353**, 133-138 (1999).
- Davenport, A.P., et al., International Union of Pharmacology. XXIX. Update on endothelin receptor nomenclature., *Pharmacol. Rev.*, **54**, 219-226 (2002).
- Douglas, S.A. and Ohlstein, E.H., Signal transduction mechanisms mediating the vascular actions of endothelin., *J. Vasc. Res.*, **34**, 152-164 (1997).
- Guisse, T., et al., Endothelins in bone cancer metastases., *Cancer Treat. Res.*, **118**, 197-212 (2004).
- Masaki, T., Historical Review: Endothelin., *Trends Pharmacol. Sci.*, **25**, 219-224 (2004).
- Mulder, P., et al., Selective endothelin-A versus combined endothelin-A/endothelin-B receptor blockade in rat chronic heart failure., *Circulation*, **102**, 491-493 (2000).
- Opgenorth, T.J., et al., Pharmacological characterization of A-127722: An orally active and highly potent ET_A-selective receptor antagonist., *J. Pharmacol. Exp. Ther.*, **276**, 473-481 (1996).
- Opgenorth, T.J., Endothelin receptor antagonism., *Adv. Pharmacol.*, **33**, 1-65 (1995).
- Peter, M.G. and Davenport, A.P., Selectivity of [¹²⁵I]-PD151242 for human, rat and porcine endothelin ET_A receptors in the heart., *Br. J. Pharmacol.*, **114**, 297-302 (1995).
- Watakabe, T., et al., A reversible radioligand specific for the ET_B receptor: [¹²⁵I] Tyr¹³-Suc-[Glu⁹, Ala¹¹, ¹⁵]-endothelin-1 (8-21), [¹²⁵I] IRL 1620., *Biochem. Biophys. Res. Commun.*, **185**, 867-873 (1992).
- Yanagisawa, M., et al., A novel, potent vasoconstrictor peptide produced by vascular endothelial cells., *Nature*, **332**, 411-415 (1988).

Overview

Endothelins are a family of vasoactive peptides that were discovered in a search for the identity of a vasoconstricting factor known to exist in the media from cultured endothelial cells. The first member of this family, endothelin-1 or ET-1, was revealed in a seminal Nature article published in March, 1988. Subsequently, ET-2, ET-3 and several snake venom toxins, called sarafotoxins, were identified as members of a structurally defined family of bicyclic 21 amino acid peptides.

The mammalian peptides, ET-1 and ET-3, are produced by a wide range of tissues and cells. ET-1 is the primary isoform circulating in plasma. ET-3 has been found in high levels in brain. ET-2 may be more selectively produced in the kidney and intestine, but its functional significance remains poorly defined. The endothelins are all coded from separate genes and the gene products require proteolytic processing to produce mature endothelins. A number of endothelin converting enzymes (ECE) have been identified that may be important in the final proteolytic activating step.

The endothelins function through their interaction with G protein-coupled receptors. To date, two subtypes have been cloned from mammalian cells, ET_A and ET_B. The ET_A receptors have a much greater affinity for ET-1 over ET-3 and are expressed abundantly in vascular smooth muscle and stromal tissues. In humans and animals, *in vivo* and *in vitro* studies with selective antagonists have revealed that the vasoconstrictor and proliferative effects of ET-1 are primarily mediated by the ET_A receptor. The ET_B receptor binds both ET-1 and ET-3 with nearly equal affinity and is expressed abundantly on endothelial cells and epithelial tissues. While the ET_B receptor can mediate

a vasoconstrictor response, its physiological role appears to be two-fold: i) mediation of ET-1-induced nitric oxide release from endothelial cells and an accompanying vasodilation response, and ii) clearance of ET peptides from the circulation. These conclusions are supported by studies with ET_B-selective antagonists that block the transient vasodilation response observed upon bolus intravenous administration of ET-1 or studies showing that hypertension is associated with chronic administration of ET_B antagonists, and the marked increase in plasma endothelin levels upon ET_B-selective or non-selective receptor blockade, but not ET_A-selective blockade. In addition to their vasoactive properties, these receptors are involved in regulation of cell proliferation. Gene disruption studies indicate that both receptor subtypes and, ET-1 and ET-3 peptides, play important roles in embryologic development.

Perhaps the most interesting area of ET research to emerge in the last few years relates to the potential role of ET in the regulation of bone growth. ET-1, via ET_A receptors, has been found to stimulate osteoblast activity resulting in abundant and disorganized new bone characteristic of osteoblastic metastases. The connection between tumors that produce excessive ET-1 and metastatic bone disease is intriguing and has led to an interest in utilizing ET receptor antagonists to treat prostate cancer.

Therapeutic interest in blocking the endothelin system has been high, leading to the discovery of a large number of peptidic and non-peptide receptor antagonists. These antagonists may have utility in a number of cardiovascular diseases, including congestive heart failure, pulmonary hypertension,

stroke, kidney failure, hypertension, angioplasty-induced restenosis, and a variety of non-cardiovascular conditions, such as asthma, chronic obstructive pulmonary disease, pain and cancer. Atrasentan is in Phase III trials for treatment of advanced prostate cancer. Bosentan (Tracleer®) is marketed for treatment of primary pulmonary arterial hypertension.

Endothelin Receptors

CURRENTLY ACCEPTED NAME	ET _A (E7155)	ET _B
STRUCTURAL INFORMATION	427 aa (human)	442 aa (human)
PREFERRED ENDOGENOUS PEPTIDES	ET-1 (E7764) = ET-2 (E9012) >> ET-3 (E9137)	ET-1 (E7764) = ET-2 (E9012) = ET-3 (E9137)
SUBTYPE SELECTIVE AGONISTS	Not known	[Ala ^{1,3,11,15}]-ET-1 (E6877), Sarafotoxin S6c (S6545, S157), IRL-1620 (E137), BQ-3020 (E139),
SUBTYPE SELECTIVE ANTAGONISTS ^a	A-127722, ^b A-147627 (ABT 627, Atrasentan), A-216546, BQ-123 (B150), BQ-610 (B151), FR 139317, Lu-135252 (Darusentan), PD 151,242 (P208), PD 156,707, TBC-11251 (Sitaxsentan)	A-192621, BQ-788 (B157), RES-701-1 (R4027), Ro 46-8443
NON-SELECTIVE ANTAGONISTS	A-182086, Ro-61-6612 (Tezosentan), SB-209670, SB-217242 (Enrasentan), PD 142,893 (P2959), PD 145,065 (P3084), Ro 47-0203 (Bosentan)	A-182086, Ro-61-0612 (Tezosentan), SB 209670, SB-217242, PD 142,893 (P2959), PD 145,065 (P3084), Ro 47-0203 (Bosentan)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG) ^c	G _{q/11} (increase IP ₃ /DAG) ^c
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-ET-1, [³ H]-BQ-123	[¹²⁵ I]-ET-1, [¹²⁵ I]-ET-3
TISSUE EXPRESSION	Widespread: higher in vascular and stromal cells	Widespread: higher in endothelial and epithelial cells
PHYSIOLOGICAL FUNCTION	Vasoconstriction, proliferation	ET-1 clearance
DISEASE RELEVANCE	Cardiovascular, renal, cancer	Not known

Abbreviations

A-127722: trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

A-147627 (ABT-627): (2R,3R,4S)-(+)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

A-186086: (2R,3R,4S)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonfylamino)ethyl)-pyrrolidine-3-carboxylic acid

A-192621: (2R,3R,4S)-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylamino-carbonylmethyl)-pyrrolidine-3-carboxylic acid

A-216546: [2S-(2,2-Dimethylpentyl)-4S-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3R-carboxylic acid

BQ-123: cyclo (D-α-Aspartyl-L-prolyl-D-valyl-L-leucyl-D-tryptophyl)

BQ-610: N-[1-Formyl-N-[N-[(hexahydro-1H-azepin-1-yl)carbonyl]-L-leucyl]-D-tryptophyl]-D-tryptophan

BQ-788: N-[N-[N-[(2,6-Dimethyl-1-piperidyl)carbonyl]-4-methyl-L-leucyl]-1-(methoxycarbonyl)-D-tryptophyl]-D-norleucine

BQ-3020: N-Acetyl-[Ala^{11,15}]-Endothelin-1(6-21)

ET-1: Endothelin-1

ET-2: Endothelin-2

ET-3: Endothelin-3

FR 139317: (R)-2-[(R)-2-[(S)-2-[[1-(Hexahydro-1H-azepinyl)carbonyl]amino-4-propionyl]amino-3-(2-pyridyl)propionic acid

IRL 1620: N-Suc-[Glu⁹,Ala^{11,15}]-Endothelin-1(8-21)

Lu 13552: (+)-(S)-2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenyl-propionic acid

PD 142,893: N-Acetyl-β-Phenyl-D-Phe-Leu-Asp-Ile-Ile-Trp

PD 145,065: N-Acetyl-α-[10,11-Dihydro-5H-dibenzo[a,d]cycloheptadien-5-yl]-D-Gly-Leu-Asp-Ile-Ile-Trp

PD 151,242: N-[N-[N-[(Hexahydro-1H-azepin-1-yl)carbonyl]-L-leucyl]-1-methyl-D-tryptophyl]-D-tyrosine

PD 156,707: Sodium 2-benzo[1,3]dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoate

RES-701-1: cyclic (Gly¹-Asp⁹) (Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp-Trp-Phe-Phe-Asn-Tyr-Tyr-Trp)

Ro 46-8443: N-[6-[(2R)-2,3-Dihydroxypropoxy]-5-(2-methoxyphenoxy)-2-(4-methoxyphenyl)-4-pyrimidinyl]-4-(1,1-dimethylethyl)-benzenesulfonamide

Ro 47-0203: 4-Tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulfonamide

Ro 61-0612: 5-Isopropyl-pyridine-2-sulfonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide

SB-209670: (±)-(1S,2R,3S)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid

SB-217242: 1-(1,3-Benzodioxol-5-yl)-2,3-dihydro-3-[2-(2-hydroxyethoxy)-4-methoxyphenyl]-5-propoxy-,1H-indene-2-carboxylic acid

TBC-11251: N-(4-Chloro-3-methyl-5-isozazolyl)-2-[(6-methyl-1,3-benzodioxol-5-yl)acetyl]-3-thiophenesulfonamide

FOOTNOTES

a "Subtype Selective Antagonists" means > 500-fold.

b A-127722 is the racemic version of A-147627 (ABT-627, Atrasentan).

c Some evidence exists to suggest that endothelin receptors may signal through other signal transduction mechanisms.