

Endothelin

Overview: Endothelin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Endothelin Receptors, Davenport, 2002) are activated by the endogenous 21 amino-acid peptides endothelin-1 (ET-1, ENSG00000078401), ET-2 (ENSG00000127129) and ET-3 (ENSG00000124205). Non-selective peptide (e.g. TAK044, pA₂ 8.4) and non-peptide (e.g. bosentan, pA₂ 6.0–7.2; SB209670, pA₂ 9.4) antagonists can block both ET_A and ET_B receptors. Splice variants of the ET_A receptor have been identified in rat pituitary cells; one of these, ET_{AR}-C13, appeared to show loss of function with comparable plasma membrane expression (Hatae et al., 2007).

Nomenclature	ET _A	ET _B
Ensembl ID	ENSG00000151617	ENSG00000136160
Principal transduction	G _{q/11} , G _s	G _{q/11} , G _{i/o}
Potency order	ET-1, ET-2 > ET-3 (Maguire and Davenport, 1995)	ET-1, ET-2, ET-3
Selective agonists	–	[Ala ^{1,3,11,15}]ET-1 (Molenaar et al., 1992), sarafotoxin S6c (Russell and Davenport, 1996), IRL1620 (Watakabe et al., 1992), BQ3020 (Russell and Davenport, 1996) BQ788 (8.4, Russell and Davenport, 1996), A192621 (8.1, von Geldern et al., 1999), IRL2500 (7.2, Russell and Davenport, 1996), Ro468443 (7.1, Breu et al., 1996)
Selective antagonists	A127722 (9.2–10.5, Opgenorth et al., 1996), LU135252 (8.9, Riechers et al., 1996), SB234551 (8.7–9.0, Ohlstein et al., 1998), PD156707 (8.2–8.5, Maguire et al., 1997), FR139317 (7.3–7.9, Maguire and Davenport, 1995), BQ123 (6.9–7.4, Maguire and Davenport, 1995), ZD4054 (pIC ₅₀ 8.3, Morris et al., 2005)	
Probes	[³ H]-S0139 (0.6 nM), [³ H]-BQ123 (3.2 nM, Ihara et al., 1995), [¹²⁵ I]-PD164333 (0.2 nM, Davenport et al., 1998), [¹²⁵ I]-PD151242 (0.5 nM, Davenport et al., 1994)	[¹²⁵ I]-IRL1620 (20 pM, Watakabe et al., 1992), [¹²⁵ I]-BQ3020 (0.1 nM, Molenaar et al., 1992), [¹²⁵ I]-[Ala ^{1,3,11,15}]ET-1 (0.2 nM, Molenaar et al., 1992)

Subtypes of the ET_B receptor have been proposed, although gene disruption studies in mice suggest that the heterogeneity results from a single gene product (Mizuguchi et al., 1997).

Abbreviations: A127722, *trans-trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-([N,N-dibutylamino]carbonylmethyl)pyrrolidine-3-carboxylate; A192621, (2R,3R,4S)-2-(4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-[2,6-diethylphenyl]acetamido)pyrrolidine-3-carboxylic acid; BQ123, *cyc*(DTrp-DAsp-Pro-D-Val-Leu); BQ3020, *N*-acetyl-Leu-Met-Asp-Lys-Glu-Ala-Val-Tyr-Phe-Ala-His-Leu-Ile-Ile-Trp; BQ788, *N*-*cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyl-D-norleucine; FR139317, (R)2-([R-2-((S)-2-([1-(hexahydro-1H-azepinyl)carbonyl]amino)methyl)pentanoyl]amino-3-(3-[methyl-1H-indolyl])propionylamino-3-(2-pyridyl))propionate; IRL1620, Suc[Glu⁹,Ala^{11,15}]ET-1₁₀₋₂₁; IRL2500, *N*-(3,5-dimethylbenzoyl)-*N*-methyl-(D)-(4-phenylphenyl)-Ala-Trp; LU135252, (+)-(S)-2-(4,6-dimethoxypyrimidin-2-yloxy)-3-methoxy-3,3-propionic acid; PD151242, (N-[[hexahydro-1-azepinyl]carbonyl]Leu(1-Me)-DTrp-DTyr; PD156707, 2-benzo[1,3]dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoate; PD164333, 2-benzo[1,3]dioxol-5-yl-4-(3-[2-(4-hydroxyphenyl)-ethylcarbamoyl]-propoxy)-4,5-dimethoxy-phenyl-3-(4-methoxy-benzoyl)-but-2-enoate; RES7011, *cyc*(Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp)-Trp-Phe-Phe-Asn-Tyr-Tyr-Trp; Ro468443, (R)-4-*tert*-butyl-N-(6-[2,3-dihydroxypropoxy]-5-[2-methoxyphenoxy]-2-[4-methoxyphenyl]-pyrimidin-4-yl)-benzenesulfonamide; S0139, 27-O-3-(2-[3-carboxyacryloylamino]-5-hydroxyphenyl)-acryloyloxymyricone, sodium salt; SB209670, (+)-1S,2R,S-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxypheyl)-5-prop-1-yloxyindane-2-carboxylate; SB234551, (E)-α-([1-butyl-5-[2-([2-carboxyphenyl]methoxy)-4-methoxyphenyl]-1H-pyrazol-4-yl]methylene)-6-methoxy-1,3-benzodioxole-5-propanoic acid; TAK044, *cyc*(D-Asp-Asp(Php)-Asp-D-Thg-Leu-D-Trp)-4-oxobut-2-enoate; ZD4054, *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide

Further Reading

- Bagnato A, Rosano L (2008). The endothelin axis in cancer. *Int J Biochem Cell Biol* 40: 1443–1451.
- Davenport AP (2002). International Union of Pharmacology. XXIX. Update on endothelin receptor nomenclature. *Pharmacol Rev* 54: 219–226.
- Davenport AP, Maguire JJ (2006). Endothelin. *Handb Exp Pharmacol* 176: 295–329.
- Dhaun N, Pollock DM, Goddard J, Webb DJ (2007). Selective and mixed endothelin receptor antagonism in cardiovascular disease. *Trends Pharmacol Sci* 28: 573–579.
- Dhaun N, Goddard J, Kohan DE, Pollock DM, Schiffrin EL, Webb DJ (2008). Role of endothelin-1 in clinical hypertension: 20 years on. *Hypertension* 52: 452–459.
- Dupuis J, Hoeper MM (2008). Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 31: 407–415.
- Khodorova A, Montmayeur JP, Strichartz G (2009). Endothelin receptors and pain. *J Pain* 10: 4–28.
- Kirkby NS, Hadoke PW, Bagnall AJ, Webb DJ (2008). The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? *Br J Pharmacol* 153: 1105–1119.
- Motte S, McEntee K, Naeije R (2006). Endothelin receptor antagonists. *Pharmacol Ther* 110: 386–414.
- Schinelli S (2006). Pharmacology and physiopathology of the brain endothelin system: an overview. *Curr Med Chem* 13: 627–638.
- Schneider MP, Boesen EL, Pollock DM. (2007). Contrasting actions of endothelin ET_A and ET_B receptors in cardiovascular disease. *Annu Rev Pharmacol Toxicol* 47: 731–759.
- Schorlemmer A, Matter ML, Shohet RV (2008). Cardioprotective signaling by endothelin. *Trends Cardiovasc Med* 18: 233–239.

References

- Breu V et al. (1996). *FEBS Lett* 383: 37–41.
- Davenport AP et al. (1994). *Br J Pharmacol* 111: 4–6.
- Davenport AP et al. (1998). *Br J Pharmacol* 123: 223–230.
- Hatae N et al. (2007). *Mol Endocrinol* 21: 1192–1204.

- Ihara M *et al.* (1995). *Eur J Pharmacol* **274**: 1–6.
- Maguire JJ, Davenport AP (1995). *Br J Pharmacol* **115**: 191–197.
- Maguire JJ *et al.* (1997). *J Pharmacol Exp Ther* **280**: 1102–1108.
- Mizuguchi T *et al.* (1997). *Br J Pharmacol* **120**: 1427–1430.
- Molenaar P *et al.* (1992). *Br J Pharmacol* **107**: 637–639.
- Morris CD *et al.* (2005). *Br J Cancer* **92**: 2148–2152.
- Ohlstein EH *et al.* (1998). *J Pharmacol Exp Ther* **286**: 650–656.
- Opigenorth TJ *et al.* (1996). *J Pharmacol Exp Ther* **276**: 473–481.
- Riechers H *et al.* (1996). *J Med Chem* **39**: 2123–2128.
- Russell FD, Davenport AP (1996). *Br J Pharmacol* **119**: 631–636.
- von Geldern TW *et al.* (1999). *J Med Chem* **42**: 3668–3678.
- Watakabe T *et al.* (1992). *Biochem Biophys Res Commun* **185**: 867–873.