

Leukotriene Receptors

Key References

- Beller, T.C., et al., Targeted gene disruption reveals the role of the cysteinyl leukotriene 2 receptor in increased vascular permeability and in bleomycin-induced pulmonary fibrosis in mice., *J. Biol. Chem.*, **279**, 46129-46134 (2004).
- Brink, C., et al., International Union of Pharmacology XXXVII. Nomenclature for leukotriene and lipoxin receptors., *Pharmacol. Rev.*, **55**, 195-227 (2003).
- Heise, C.E., et al., Characterization of the human cysteinyl leukotriene 2 receptor., *J. Biol. Chem.*, **275**, 30531-30536 (2000).
- Kelloway, J.S., Zafirlukast: The first leukotriene-receptor antagonist approved for the treatment of asthma., *Ann. Pharmacother.*, **31**, 1012-1021 (1997).
- Lynch, K.R., et al., Characterization of the human cysteinyl leukotriene CysLT receptor., *Nature*, **399**, 789-793 (1999).
- Metters, K.M., Leukotriene receptors., *J. Lipid Mediators Cell Signal.*, **12**, 4113-4127 (1995).
- Penning, T.D., Freland, D.J., Recent advances in leukotriene B4 receptor antagonist research., *Exp. Opin. Ther. Patents*, **6**, 21-28 (1995).
- Tager, A.M., et al., Leukotriene B4 receptor BLT1 mediates early effector T cell recruitment., *Nat. Immunol.*, **4**, 982-990 (2003).
- Tudhope, S.R., et al., Bayu9773, a novel antagonist of cysteinyl-leukotrienes with activity against two receptor subtypes., *Eur. J. Pharmacol.*, **264**, 317-323 (1994).
- Walch, L, et al., Pharmacological evidence for a novel cysteinyl leukotriene receptor subtype in human pulmonary artery smooth muscle., *Br. J. Pharmacol.*, **137**, 1339-1345.
- Yokomizo, T., et al., A G protein-coupled receptor for leukotriene B4 that mediates chemotaxis., *Nature*, **387**, 620-624 (1997).
- Yokomizo, T., et al., Hydroxyeicosanoids bind to and activate the low affinity leukotriene B4 receptor, BL2., *J. Biol. Chem.*, **276**, 12454-12459 (2001).

Overview

Leukotrienes (LTs) exist as two distinct classes, hydroxyacids such as LTB₄, and cysteinyl leukotrienes such as LTC₄, LTD₄ and LTE₄. Leukotriene receptors have been classified into BLT and CysLT types to signify this basic level of selectivity, but there is also heterogeneity within both classes. Thus, there are two subtypes of both BLT, termed BLT₁ and BLT₂, and CysLT, termed CysLT₁ and CysLT₂. There may also be further subdivision of CysLT receptors, but this remains to be confirmed. The classification into types and subtypes of LT receptor was based initially on functional data, using the natural agonists and a wide range of antagonists. While LTB₄ may be regarded as a selective agonist at BLT receptors, and cysteinyl LTs are selective agonists at CysLT receptors, no subtype-selective agonist has been reported for BLT₁ or either CysLT receptor. Furthermore, despite the availability of a plethora of antagonists at both BLT receptors and CysLT₁ receptors, no selective antagonist has yet been reported for CysLT₂ receptors. The only compound reported to exhibit antagonist activity at this receptor is the non-selective CysLT antagonist, BAYu9773. The evidence for further subdivision of CysLT receptors is that responses of human and porcine pulmonary artery to cysteinyl LTs are resistant to CysLT₁ and CysLT₂ antagonists.

BLT₁, BLT₂, CysLT₁ and CysLT₂ receptors have now all been cloned; the first was the human BLT₁ receptor in 1999 from an HL-60 cell cDNA library, and shown to be a G protein-coupled receptor that had erroneously been identified as the P2Y₇ purinoceptor. Interestingly, the promoter for the BLT₁ receptor was later found to lie in the open reading frame of the gene for the BLT₂ receptor. The CysLT₁ and the CysLT₂ receptors, both cloned in 2000,

again proved to be members of the G protein-coupled receptor superfamily. LT receptors may couple, albeit not exclusively, via G_i to inhibit adenylate cyclase, and G_{q/11} to modulate inositol phospholipid hydrolysis and calcium mobilization.

Studies variously using agonists, antagonists and gene deletion all suggest that LTs are important pro-inflammatory mediators, although the specific actions mediated by BLT and CysLT receptors are quite distinct. BLT receptors primarily mediate chemoattraction; BLT agonists being highly potent in the recruitment of neutrophils and to a lesser extent eosinophils to sites of inflammation. Like other chemotactic agents, such as fMLP, they also appear to induce the release of lysosomal enzymes and superoxide anion. BLT agonists appear to have no direct effects on smooth muscle, and although they have been shown to elicit a contraction of airway smooth muscle in the guinea pig, this effect appears to be secondary to phospholipase C-induced mobilization of arachidonic acid from membrane phospholipids, and subsequent prostanoid generation. Despite the association between BLT receptors and the activation of inflammatory cells, disappointing clinical findings suggest that selective BLT receptor antagonists are of limited use in the treatment of asthma.

CysLT receptors mediate a range of other pro-inflammatory effects, such as constriction of airways and vascular smooth muscle, increased endothelial membrane permeability, leading to plasma exudation and edema, and an enhanced secretion of thick, viscous mucus. The cysteinyl LTs have been implicated in various inflammatory diseases, notably asthma. It is believed that the adverse effects observed with non-

steroidal anti-inflammatory agents (cyclooxygenase inhibitors), in conditions such as asthma and inflammatory bowel disease, result at least in part from an enhancement of LT release through the removal of a prostanoid-induced suppression. The development of potent, long acting, orally active CysLT receptor blocking drugs, such as zafirlukast, montelukast, and pranlukast, has provided evidence for a role of CysLT receptors in asthma; these compounds now being increasingly regarded as useful additions to the therapeutic armory in the treatment of this disease.

Leukotriene Receptors

CURRENTLY ACCEPTED NAME	BLT ₁	BLT ₂	CysLT ₁	CysLT ₂
ALTERNATE NAME	None	None	None	None
STRUCTURAL INFORMATION	352 aa (human)	358 aa (human)	338 aa (human)	347 aa (human)
SUBTYPE SELECTIVE AGONISTS	Not known	12(S)-oxoETE 15(S)-HETE (H1142)	LTD ₄ (L5011)	BAYu9773 (B9680) ^a
SUBTYPE SELECTIVE ANTAGONISTS	U-75302 (U1508), 20-Carboxy-LTB ₄ , LTB ₄ -aminopropylamide, CP-105696	LY-255283	Montelukast, Zafirlukast, Pranlukast, Cinalukast (C6293), Pobilukast, SKF 104353, LY-170680, BAYx7195, ZD 3523	Not known
RECEPTOR SELECTIVE AGONISTS	LTB ₄ (L0517)	LTB ₄ (L0517)	LTC ₄ (L4886)	LTC ₄ (L4886)
RECEPTOR SELECTIVE ANTAGONISTS	ZK 158252, CP 195543, RG 14893, ^b SB-209247, ^b SC-53228, ^b ONO 4057, ^b CGS25019C, ^b RP 69698, ^b LY-293111 ^b	ZK 158252, CP 195543	BAYu9773 (B9680)	BAYu9773 (B9680) ^a
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation)	G _i (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[³ H]-LTD ₄ , [³ H]-CGS23131	[³ H]-LTB ₄	[³ H]-LTD ₄ , [³ H]-ICI 198,615	Not known
TISSUE EXPRESSION	Leukocytes	Ubiquitous	Leukocytes, various broncho- pulmonary tissues	Leukocytes, heart adrenal medulla
PHYSIOLOGICAL FUNCTION	Inflammation, T cell recruitment	Not known	Inflammation, Contraction	Endothelial function
DISEASE RELEVANCE	Inflammatory	Not known	Asthma, allergy	Not known

Abbreviations

BAYu9773: 6(R)-(4'-Carboxyphenylthio)-5(S)-hydroxy-7(E),9(E),11(Z),14(Z)-eicosatetraenoic acid

BAYx7195: (4S)-[4-Carboxyphenylthio]-7-[4-(4-phenoxybutoxy)-phenyl]-hept-5-(z)-enoic acid

CGS23131: 5-(3-Carboxybenzoyl)-2-((6-(4-methoxyphenyl)-5-hexenyl)oxy)benzenepropanoic acid

CGS25019C: 4-(5-[4-(Aminoiminomethyl)phenoxy]-pentoxy)-3-methoxy-N,N-bis(1-methylethyl)-benzamide-(Z)-2-butenedioate

CP-105696: (+)-1-(3S,4R)-[3-(4-Phenyl-benzyl)-4-hydroxy-chroman-7-yl] cyclopentane carboxylic acid

CP-195543: 2-[(3S,4R)-3,4-Dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl)benzoic acid

ICI 198,615: [1-[2-Methoxy-4-[(phenylsulfonyl)amino]carbonyl]phenyl]methyl]-1H-indazol-6-yl]-carbamic acid cyclopentyl ester

LY-170680 (Sulukast): 3-(((1R,2E,4Z)-1-((aS)-a-Hydroxy-m-1H-tetrazol-5-yl)benzyl)-2,4-tetradecadienyl)thio)propionic acid

LY-255283: 1-[5-Ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone

LY-293111: 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid

ONO 4057: 5-[2-(2-Carboxyethyl)-3-[6-(4-Methoxyphenyl)-5E-hexenyl]oxyphenoxy]valeric acid

RG 14893: 4-(2-(Methyl(2-phenethyl)amino)-2-oxoethyl)-8-(phenylmethoxy)-2-naphthalenecarboxylic acid

RP 69698: 2-[[5-Methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenylpyridine

SB-209247: (E)-3-[6-[[2,6-Dichlorophenyl]thio]methyl]-3-(2-phenylethoxy)-2-pyridinyl]-2-propenoic acid

SC 53228: (+)-(S)-7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid

SKF 104353: 2-Hydroxy-3-carboxyethylthio-3-[2-(8-phenyloctyl)phenyl]propanoic acid

U-75302: (5S)-6-[6-[(1E,3R,5Z)-3-Hydroxy-1,5-undecadienyl]-2-pyridinyl]-1,5-hexanediol

ZD 3523: 4-[[5-[(2R)-2-Methyl-4,4,4-trifluorobutyl]carbonyl]-1-methylindol-3-yl]methyl]-3-methoxy-N-[(2-methylphenyl)sulfonyl]benzamide

ZK 158252: 5-[2-[5-Hydroxy-5-[1-(3-phenyl-2-propynyl)cyclobutyl]-1,3-pentadienyl]cyclohexylidene]pentanoic acid

FOOTNOTES

^a BAYu9773 has been reported to demonstrate partial agonist activity at recombinant CysLT₂ receptors.

^b Affinity for BLT₂ receptors not reported.