Leukotriene, lipoxin, oxoeicosanoid and resolvin E1

Overview: Leukotriene receptors (nomenclature agreed by NC-IUPHAR subcommittee on Leukotriene and Lipoxin Receptors, Brink *et al*., 2003) are activated by the endogenous ligands leukotriene (LT) B_4, LTC_4, LTD_4, LTE_4, 12*R*-HETE and 12*S*-HETE. Lipoxin A_4 receptors (FPR2/ALX, nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors; Ye *et al*., 2009) are activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A_4 (LXA_4) and 15-epi-LXA_4 (aspirin-triggered lipoxin A_4, ATL). Oxoeicosanoid receptors (OXE, nomenclature agreed by NC-IUPHAR on Oxoeicosanoid Receptors; Brink *et al*., 2004) are activated by endogenous chemotactic eicosanoid ligands oxidized at the C-5 position, with 5-oxo-ETE the most potent agonist identified for this receptor. Resolvin receptors (provisional nomenclature) are activated by the lipid-derived, anti-inflammatory ligand resolvin E1 (RvE1), which is the result of sequential metabolism of EPA by aspirin-modified cyclooxygenase and lipoxygenase (Arita *et al*., 2005a,b).

$CysLT_1$ and $CysLT_2$ are co-expressed by most myeloid cells. However, the function of $CysLT_2$ remains unclear. $CysLT_2$ has been demonstrated to exert a suppressive influence on $CysLT_1$ expression, suggesting an autoregulatory function that is indicated by a reported up-regulation of CysLT-mediated responses in mice lacking $CysLT_2$ receptors (Jiang *et al*., 2007).

Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-*S*-transferase/LTC_4 synthase, γ-glutamyltranspeptidase and several aminopeptidases) and can also bind to peroxisome proliferator-activated receptor α (PPARα, Lin *et al*., 1999) and the FPR2/ALX lipoxin receptor (Fiore *et al*., 1994), complicating the interpretation of radioligand binding and functional studies (e.g. LTC_4 is rapidly converted in many systems to LTD_4). Metabolic inhibitors (e.g. serine–borate complex) reduce this problem but can also have nonspecific effects. The FPR2/ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide (Chiang *et al*., 2000) as well as annexin 1 (ANXA1) and its *N*-terminal peptides (Perretti *et al*., 2002). In addition, a soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has been reported to activate the FPR2/ALX receptor (Resnati *et al*., 2002). Furthermore, FPR2/ALX has been suggested to act as a receptor mediating proinflammatory actions of the acute-phase reactant, serum amyloid A (Su *et al*., 1999; Sodin-Semrl *et al*., 2004).

Nomenclature	BLT_1	BLT_2	$CysLT_1$	$CysLT_2$
Other names	LTB_4	–	HG55, HMTMF81, LTD_4	HPN321, LTC_4
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	LTB_4 > 20-hydroxy-LTB_4 >> 12*R*-HETE (Yokomizo *et al*., 2001)	LTB_4 > 12*S*-HETE = 12*S*-HPETE > 15*S*-HETE>12*R*-HETE = 15*S*-HETE > 20-hydroxy-LTB_4 (Yokomizo *et al*., 2001)	LTD_4 > LTC_4 > LTE_4 (Sarau *et al*., 1999)	LTC_4 = LTD_4 >> LTE_4 (Nothacker *et al*., 2000)
Selective agonists	–	12*S*-HETE	–	BAYu9773
Selective antagonists	CP105696 (pIC_{50} 7.2), U75302 (pIC_{50} 6.9)	LY255283 (pIC_{50} 6.0)	Zafirlukast (9.5), montelukast (9.3), SR2640 (8.7), pobilukast (8.6), sulukast (8.3)	–
Probes	[^{3}H]-LTB_4 (0.2–0.7 nM), [^{3}H]-CGS23131 (13 nM)	[^{3}H]-LTB_4 (0.2–23 nM)	[^{3}H]-LTD_4, [^{3}H]-ICI198615	[^{3}H]-LTD_4

BAYu9773 is an antagonist at $CysLT_1$ (6.8–7.7) and a reduced efficacy agonist at $CysLT_2$ receptors. The $CysLT_1$ and $CyLT_2$ receptors also respond to uracil nucleotides (Mellor *et al*., 2001; 2003). GPR17 has been described as a 'dualistic' receptor responding to both uracil nucleotides and cysteinyl leukotrienes, responses that may be inhibited by antagonists of either P2 or CysLT receptors (Ciana *et al*., 2006).

Nomenclature	FPR2/ALX	OXE	RvE1
Other names	FPRL1, FPR2, FPRH2, RFP, ALX	TG1019 (Hosoi *et al*., 2002), R527 (Jones *et al*., 2003), hGPCR48 (Koike *et al*., 2006)	ChemR23, chemokine receptor-like 1, DEZ
Ensembl ID	ENSG00000171049	ENSG00000162881	ENSG00000174600
Principal transduction	G_i (Maddox *et al*., 1997)	$G_{i/o}$ (O'Flaherty *et al*., 2000; Hosoi *et al*., 2002; Jones *et al*., 2003; Hosoi *et al*., 2005)	Not yet established
Rank order of potency	LXA_4 = ATL = ATLa2 > LTC_4 = LTD_4 >> 15-deoxy-LXA_4 >> fMLP (Fiore *et al*., 1994; Fiore and Serhan, 1995; Takano *et al*., 1997; Clish *et al*., 1999; Gronert *et al*., 2001)	5-Oxo-ETE, 5-oxo-C20:3 >> 5*S*-HpETE > 5*S*-HETE (Hosoi *et al*., 2002; Jones *et al*., 2003; Patel *et al*., 2008)	RvE1 > chemerin C-terminal peptide > 18*R*-HEPE > EPA (Arita *et al*., 2005a,b)
Selective agonists	LXA_4, ATL, ATLa2 (Guilford *et al*., 2004)	5-Oxo-ETE	–
Probes	[^{3}H]-LXA_4 (0.2–1.7 nM; Fiore *et al*., 1994; Takano *et al*., 1997)	[^{3}H]-5-oxo-ETE (3.8 nM, O'Flaherty *et al*., 1998)	[^{3}H]-RvE1 (11 nM, Arita *et al*., 2007)

A receptor selective for LXB_4 has been suggested from functional studies (Maddox and Serhan, 1996; Romano *et al*., 1996; Ariel *et al*., 2003). Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as DHA and EPA, acted as receptor antagonists (Hosoi *et al*., 2002).

Abbreviations: 5-oxo-C20:3, 5-oxo-6*E*,8*Z*,11*Z*-eicosatrienoic acid; **5-oxo-ETE**, 5-oxo-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; **12*r*-HETE**, 12*R*-hydroxyeicosa-5*Z*,8*Z*,10*E*,14*Z*-tetraenoic acid; **18*r*-HEPE**, 18*R*-hydroxyeicosapentaenoic acid; **5*s*-HETE**, 5*S*-hydroxy-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; **5*s*-HpETE**, 5*S*-hydroperoxy-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid; **ANXA1**, annexin 1; **ATL**, aspirin-triggered lipoxin A_4 [15-*epi*-LXA_4, 5*S*,6*R*,15*R*-trihydroxyl-7*E*,9*E*,13*E*,11*Z*-eicosatetraenoic acid]; **ATLa2**, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA_4]; **BAYu9773**, 6(*R*)-(4′-carboxyphenyl-thio)-5(*S*)-hydroxy-7*E*,11*Z*,14*Z*-eicosatetraenoic acid; **CGS23131**, (*E*)-5-(3-carboxybenzoyl)-2-([6-{4-methoxyphenyl}-5-hexenyl]oxy)benzene propanoic acid; also known as LY223982; **CP105696**, (+)-1-(3S,4R)-[3-(4-phenylbenzyl)-4-hydroxy-chroman-7-yl]cyclopentane carboxylic acid; **DHA**, 4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*-docosahexaenoic acid; **EPA**, 5*Z*,8*Z*,11*Z*,14*Z*,17*Z*-eicosapentaenoic acid; **ICI198615**, (1-[2-methoxy-4-{([phenylsulfonylamino]carbonyl)phenyl}methyl]-1*H*-indazol-6-yl)carbamic acid cyclopentyl ester; **LTC_4**, leukotriene C_4; **LTD_4**, leukotriene D_4; **LXA_4**, lipoxin A_4 [5S,6R,15S-trihydroxyl-7E,9E,13E-11Z-eicosatetraenoic acid]; **LY255283**, 1-(5-ethyl-2-hydroxy-4-[{6-methyl-6-(1H-tetrazol-5-yl)-heptyl}-oxy]-phenyl)-ethanone; **OXE**, oxoeicosanoid; **RvE1**, resolvin E1 or 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-EPA; **SR2640**, 2-(3-[2-quinolylmethoxy]phenylamino)benzoic acid; **U75302**, 6-(6-(3-hydroxy-1*E*,5*Z*-undecadien-1-yl)-2-pyridinyl)-1,5-hexanediol

Further Reading

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