

Lysophospholipid Receptors

Key References

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Overview

Although historically considered as intermediates in the biosynthesis of glycerophospholipids and the degradation of sphingolipids, the lysophospholipids lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P) together form a class of extracellular mediators that evoke a wide range of biological responses. LPA is generated extracellularly by the concerted action of several phospholipases on plasma lipids while S1P is generated by sphingosine kinases and released from cells by unknown mechanisms. LPA and S1P are both produced by thrombin stimulation of platelets and can accumulate in serum in low micromolar concentrations. In addition, LPA has been shown to accumulate in other body fluids under pathological conditions; for example, in the ascites of ovarian cancer patients.

Due to their high potency (EC₅₀ 1-100 nM) and their ability to elicit responses when applied extracellularly, as well as the sensitivity of many responses to pertussis toxin, it was proposed that both LPA and S1P mediated their effects via their interaction with G protein-coupled receptors (GPCRs). Thus, the identification of a set of LPA/S1P G protein-coupled receptors, referred to as the 'Edg' cluster (Endothelial differentiation gene), was a seminal event in understanding the biology of these mediators. As expected from consideration of other groups of GPCRs, the LPA receptors (LPA₁, LPA₂ and LPA₃; formerly Edg-2, Edg-4 and Edg-7, respectively) are most similar to one another (55% identical amino acids). These receptors are strongly LPA-preferring and are not activated by S1P or phosphatidic acid (at concentrations up to 10 μM). Likewise, a variety of lysophospholipids with head groups have much lower potencies and efficacies.

The other five lysophospholipid receptors (S1P₁₋₅; formerly Edg-1, Edg-5, Edg-3, Edg-6 and Edg-8, respectively) are S1P-preferring and are also most similar to one another (50% identical amino acids). Each of the S1P receptors has been subjected to binding analyses and the K_d values have been reported to be in the 2-60 nM range. Dihydro S1P (sphinganine 1-phosphate) is nearly equipotent with S1P, while addition of a choline head group (sphingosylphosphorylcholine; SPC) results in a molecule that, while active at the receptors, is distinctly less potent and less efficacious at all S1P receptor types. Phyto S1P is reported to be a high affinity ligand for the S1P₄ receptor. Other sphingolipids and glycerol-based lysophospholipids (including LPA) are inactive at the S1P receptors at concentrations up to 10 μM.

The two fundamental strategies used to understand the biology/pathology associated with the LPA/S1P receptors are mouse genetics and chemical biology. Ablation of individual receptor genes in the germ lines of mice resulted in no obvious phenotype (S1P₃, LPA₂), reduced litter size (S1P₂) with perinatal lethality and runting (LPA₁), embryonic lethality (S1P₁) or a defect of implantation (LPA₃). The defect in the S1P₁ receptor gene 'knock-out' mice was due to failure of developing blood vessels to become invested with pericytes and smooth muscle cells when the S1P₁ receptor was lacking in the endothelium. Mice with altered S1P₄ or S1P₅ receptor genes have not been reported. A zebrafish with a developmental cardiac defect has an underlying S1P receptor mutation, but the additional S1P receptor genes in fish (Takifugu rubripes has at least six) and evolutionary distance make a direct correlation to mammals impossible. Genetic analyses are hampered also by the apparent lack of LPA/S1P receptors in non-vertebrate animals.

The pro-motility, pro-mitogenic and anti-apoptotic responses to LPA and/or S1P have long fueled speculation that interference with their signaling via a small molecule receptor antagonist might be a useful anti-neoplastic strategy. However, this idea has yet to be reduced to practice in standard xenograft nude mouse models. Rather it was a S1P receptor agonist that proved most instructive. The lead compound is FTY720, which is a sphingosine analog that is being developed for use as an immune system modulator in organ transplant and autoimmune disease settings. FTY720 was found to be a pro-drug with phosphorylation by sphingosine kinase type 2 yielding the active molecule FTY720 phosphate (FTY720-P) that is a high affinity agonist at all S1P receptors except S1P₂. Studies with FTY720-P and follow on S1P₁ receptor agonists (e.g. SEW2871) have revealed a prominent role for S1P in lymphocyte trafficking. In a genetic correlate of this discovery, mice with the S1P₁ receptor gene disrupted in the T lymphocyte lineage exhibit a profound defect in egress of thymocytes. The recent discovery of a S1P₁/S1P₃ antagonist series (VPC23019 is the lead compound) might provide tools useful in exploring a role in S1P receptor blockade in pathophysiologic settings.

The use of a combination of LPA, a LPA₃ receptor agonist (OMPT) and a LPA₁/LPA₃ receptor antagonist (the precursor to VPC32183) has revealed that LPA₃ antagonists are protective in a mouse model of acute renal injury. LPA, at low dosages, is also protective in this model, apparently by acting at the LPA₁ receptor. It remains to be determined whether this finding will be confirmed with the aid of the appropriate genetic models.

Lysophospholipid Receptors

Lysophospholipid Receptors - Sphingosine 1-Phosphate Receptors

CURRENTLY ACCEPTED NAME	S1P ₁	S1P ₂	S1P ₃	S1P ₄	S1P ₅
ALTERNATE NAMES	EDG1, Edg-1	EDG5, Edg-5	EDG3, Edg-3	EDG6, Edg-6	EDG8, Edg-8
STRUCTURAL INFORMATION	382 aa (human)	353 aa (human)	378 aa (human)	384 aa (human)	398 aa (human)
AGONISTS	FTY720-P>S1P (S9666)> SEW2871 (S3944)	S1P (S9666)	S1P (S9666), FTY720-P	phytoS1P (P2795) > S1P, FTY720-P	S1P (S9666), FTY720-P
ANTAGONISTS	VPC23019	JTE-013	VPC23019	None	None
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG), G _i (cAMP modulation) G _{12/13} (cell migration)	G _{q/11} (increase IP ₃ /DAG), G _i (cAMP modulation) G _{12/13} (cell migration)	G _i (cAMP modulation) G _{12/13} (cell migration)	G _i (cAMP modulation) G _{12/13} (cell migration)
RADIOLIGAND OF CHOICE	[³³ P]-S1P	[³³ P]-S1P	[³³ P]-S1P	[³³ P]-phytoS1P	[³³ P]-S1P
TISSUE EXPRESSION	Ubiquitous	Ubiquitous	Ubiquitous	Lymphoid tissues	Oligodendrocytes, skin, spleen
PHYSIOLOGICAL FUNCTION	Lymphocyte trafficking vascular maturation	Fertility	Bradycardia	Not known	Not known
DISEASE RELEVANCE	Autoimmune disorders, allograft rejection	Not known	Not known	Not known	Not known

Lysophospholipid Receptors - Lysophosphatidic Acid Receptors

CURRENTLY ACCEPTED NAME	LPA ₁	LPA ₂	LPA ₃
ALTERNATE NAMES	EDG2, Edg-2	EDG4, Edg-4	EDG7, Edg-7
STRUCTURAL INFORMATION	365 aa (human)	351 aa (human)	353 aa (human)
AGONISTS	1-oleoyl LPA (L7260)	1-oleoyl LPA (L7260)	1-oleoyl LPA (L7260) > 1-palmitoyl LPA, S-OMPT (O2514)
ANTAGONISTS	VPC32183, Ki16425	Not known	VPC32183, Ki16425
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation) G _{12/13} (cell migration)	G _{q/11} (increase IP ₃ /DAG) G _i (cAMP modulation) G _{12/13} (cell migration)	G _{q/11} (increase IP ₃ /DAG) G _i (cAMP modulation)
RADIOLIGANDS OF CHOICE	Not known	Not known	Not known
TISSUE EXPRESSION	Ubiquitous	Leukocytes	Prostate, pancreas, kidney
PHYSIOLOGICAL FUNCTION	CNS development	Not known	Embryonic implantation
DISEASE RELEVANCE	Initiation of neuropathic pain	Not known	Not known

Abbreviations:

Edg: Endothelial differentiation gene

FTY720: 2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol

JTE-013: Full chemical name still to be determined

Ki16425: 3-(4-[4-(1-(2-Chlorophenyl)ethoxy)carbonyl amino]-3-methyl-5-isoxazolyl] benzylsulfanyl) propanoic acid

LPA: Lysophosphatidic acid

phytoS1P: phytoSphingosine 1-phosphate

SEW2871: 5-[4-Phenyl-5-(trifluoromethyl)-2-thienyl]-3-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazole

S1P: Sphingosine 1-phosphate

VPC23019: (R)-Phosphoric acid mono-[2-amino-2-(3-octyl-phenylcarbamoyl)-ethyl] ester

VPC32183: (S)-Phosphoric acid mono-[2-octadec-9-enoylamino-3-[4-(pyridine-2-ylmethoxy)-phenyl]-propyl] ester