

Lysophospholipid Receptors

Key References

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Overview

Although historically considered as intermediates in the biosynthesis of glycerophospholipids and the degradation of sphingolipids, recent research indicates that the lysophospholipids, lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), represent a novel class of extracellular mediators that evoke a wide range of biological responses. Both agents are released from certain cell types following stimulation, resulting in an extracellular pool that activates cells as autocrine and paracrine growth factors. LPA and S1P are both produced by platelets following thrombin stimulation 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 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 through their interaction with G protein-coupled receptors. Subsequently, the identification of a set of eight LPA/S1P G protein-coupled receptors, referred to as the 'Edg' cluster (Endothelial differentiation gene), provided a quantum leap forward in understanding these mediators. As expected from consideration of other GPCR groups, the LPA receptors (comprising Edg-2, Edg-4 and Edg-7) are most similar to one another exhibiting around 50% identical amino acids. These are strongly LPA-preferring; they are not activated by S1P or phosphatidic acid at concentrations up to 10 μ M and a variety of lysophospholipids with head groups show lowered potencies and efficacies. The limited information on LPA/S1P receptor

expression derives from RNA measurements. Edg-2 mRNA is found prominently in myelinating cells and in extracts of numerous peripheral tissues, while Edg-4 mRNA is associated with leukocytes, spleen and thymus and Edg-7 mRNA is found in extracts of prostate, heart and kidney.

The other five Edg receptors (Edg-1, Edg-3, Edg-5, Edg-6 and Edg-8) are S1P-preferring. Each of these receptors has been subjected to binding analyses and the K_d values for the recombinant S1P/Edg receptors have been reported to be in the 2-30 nM range. Dihydro S1P (sphinganine 1-phosphate) is nearly equipotent with S1P, while addition of a choline head group (sphingosylphosphorylcholine; SPC) results in a compound that, while active at the receptors, is distinctly less potent and less efficacious. Other sphingolipids and glycerol-based lysophospholipids (including LPA) are inactive at the S1P receptors at concentrations up to 10 μ M. Edg-1, Edg-3 and Edg-5 receptors are widely expressed throughout mammalian tissues and cultured cell lines; indeed, it is difficult to identify a cell line that is not responsive to S1P. Expression of Edg-8 mRNA is more restricted, with low resolution *in situ* hybridization to adult rat brain sections suggesting expression in white matter. Edg-6 RNA is found in extracts of lymphoid and hematopoietic tissue as well as lung.

Both LPA and S1P evoke a wide variety of responses from numerous types of cultured cells. Prominent among these responses are calcium mobilization, inhibition of hormone-induced increases in cAMP, activation of MAP kinase pathways, alterations in the cytoskeleton, anti-apoptosis effects and mitogenesis. These responses can, depending on the cell type,

be either pertussis toxin-sensitive or -insensitive. It is not known what fraction of LPA or S1P signaling is mediated by Edg receptors. Heterologous expression allows determination of G protein coupling, but because of the propensity for promiscuity in receptor-G protein coupling with over-expressed recombinant receptors and the lack of selective ligands, a consensus on which endogenous Edg receptors trigger individual cell responses is not yet possible.

Lysophospholipid Receptors - Sphingosine 1-Phosphate Receptors

CURRENTLY ACCEPTED NAME	Edg-1	Edg-3	Edg-5	Edg-6	Edg-8
ALTERNATE NAMES	lp _{B1}	lp _{B3}	lp _{B2} , H218, AGR16	lp _{B4}	lp _{B5} , nrg-1
STRUCTURAL INFORMATION	382 aa (human)	378 aa (human)	353 aa (human)	384 aa (human)	398 aa (human)
AGONISTS	S1P (S 9666) DihydroS1P > SPC (S 4257)	S1P (S 9666) DihydroS1P	S1P (S 9666) DihydroS1P	S1P (S 9666) DihydroS1P	S1P (S 9966) DihydroS1P > SPC (S 4257)
ANTAGONISTS	None known →				
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG), G _i (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG), G _i (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG)	G _i (cAMP modulation)
RADIOLIGAND OF CHOICE	[³³ P]-S1P	[³³ P]-S1P	[³³ P]-S1P	[³³ P]-S1P	[³³ P]-S1P

Lysophospholipid Receptors - Lysophosphatidic Acid Receptors

CURRENTLY ACCEPTED NAME	Edg-2	Edg-4	Edg-7
ALTERNATE NAMES	lp _{A1} , vzg-1	lp _{A2}	lp _{A3}
STRUCTURAL INFORMATION	365 aa (human)	351 aa (human)	353 aa (human) 354 aa (human splice variant)
AGONISTS	1-oleoyl LPA (L 7260)	1-oleoyl LPA (L 7260)	1-oleoyl LPA (L 7260) > 1-palmitoyl LPA
ANTAGONISTS	None known →		
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation)	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	None known →		

ABBREVIATIONS

Dihydro S1P: Sphinganine 1-phosphate

Edg: Endothelial differentiation gene

LPA: Lysophosphatidic acid

S1P: Sphingosine 1-phosphate

SPC: Sphingosylphosphorylcholine