Lysophospholipid (S1P) receptors in GtoPdb v.2021.2

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Abstract

Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Lysophospholipid receptors [89]) are activated by the endogenous lipid sphingosine 1-phosphate (S1P). Originally cloned as orphan members of the endothelial differentiation gene (edg) family [16, 112], the receptors are currently designated as S1P₁R through S1P₅R [69, 16, 112]. Their gene nomenclature has been codified as human S1PR₁, S1PR₂, etc. (HUGO Gene Nomenclature Committee, HGNC) and S1pr₁, S1pr₂, etc. for mice (Mouse Genome Informatics Database, MGI) to reflect species and receptor function. All S1P receptors have been knocked-out in mice constitutively and in some cases, conditionally.

S1PRs, particularly S1P₁, are expressed throughout all mammalian organ systems. Ligand delivery occurs via two known carriers (or "chaperones"): albumin and HDL-bound apolipoprotein M (ApoM), the latter of which elicits biased agonist signaling by S1P₁ in multiple cell types [18, 49]. The five S1PRs, two chaperones, and active cellular metabolism have complicated analyses of receptor ligand binding in native systems.

Signaling pathways and physiological roles have been characterized through radioligand binding in heterologous expression systems, targeted deletion of the different S1PRs, and most recently, mouse models that report in vivo S1P₁R activation [94, 96]. A crystal structure of an S1P₁-T4 fusion protein confirmed aspects of ligand binding, specificity, and receptor activation, determined previously through biochemical and genetic studies [65, 17]. Fingolimod (FTY720), the first FDA-approved drug to target any of the oral sphingolipid receptors, binds as a phosphorylated metabolite to four of the five S1PRs, and was the first oral therapy for multiple sclerosis (MS) [33]. Siponimod and ozanimod that target S1P₁ and S1P₅ are also FDA approved for the treatment of various MS forms [16, 112]. The mechanisms of action of fingolimod and other S1PR-modulating drugs now in development include binding S1PRs in multiple organ systems, e.g., immune and nervous systems, although the precise nature of their receptor interactions requires clarification [129, 35, 59, 60].

Contents

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Database links
Lysophospholipid (S1P) receptors
https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=135
Introduction to Lysophospholipid (S1P) receptors
https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=135

Receptors

S1P1 receptor
https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=275

S1P2 receptor
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S1P4 receptor
https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=278

S1P5 receptor
https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=279

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Induced cell rounding and neurite retraction are mediated by the G protein-coupled receptor Sphingosine-1-phosphate is a ligand for the G protein-coupled receptor EDG-6. (alkylimino)thiazolidin-4-one chemotype. molecule S1P4-R agonists based on (2Z,5Z)-5-((pyrrol-3-yl)methylene)-3-alkyl-2-


