Sphingosine 1-phosphate

Overview: Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid receptors; see Chun *et al.*, 2002) are activated by the endogenous lipid derivatives S1P and sphingosylphosphorylcholine (SPC). Originally identified as members of the endothelial differentiation gene (*edg*) family along with lysophosphatidic acid receptors, the gene names have recently been updated to *S1PR1*, etc. to reflect the receptor function of these proteins. S1P has also been described to act at intracellular sites (see Takabe *et al.*, 2008), although most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterologous expression systems using [^{32}P]-S1P (e.g. Okamoto *et al.*, 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of non-specific binding. Targeted deletion of several S1P receptors and key enzymes involved in S1P biosynthesis or degradation has clarified signalling pathways and physiological roles.

Nomenclature	$S1P_1$	$S1P_2$	$S1P_3$	$S1P_4$	$S1P_5$
Other names	edg1, lp_{B1}	edg5, lp_{B2}, AGR16, H218	edg3, lp_{B3}	*edg6*, lp_{C1}	*edg8*, lp_{B4}, NRG-1
Ensembl ID	ENSG00000170989	ENSG00000175898	ENSG00000186354	ENSG00000125910	ENSG00000180739
Principal transduction	$G_{i/o}$	G_q, $G_{12/13}$, G_s	G_q, $G_{i/o}$, G_s	$G_{i/o}$, $G_{12/13}$, G_s	$G_{i/o}$, $G_{12/13}$
Rank order of potency	S1P > dihydro-S1P > SPC(Okamoto *et al.*, 1998; Ancellin and Hla, 1999)	S1P > dihydro-S1P > SPC (Okamoto *et al.*, 1998; Ancellin and Hla, 1999)	S1P > dihydro-S1P > SPC (Okamoto *et al.*, 1998)	S1P > dihydro-S1P > SPC (van Brocklyn *et al.*, 2000	S1P > dihydro-S1P > SPC (Im *et al.*, 2000)
Selective agonists	SEW2871 (Sanna *et al.*, 2004), AUY954 (Pan *et al.*, 2006)	–	–	–	–
Selective antagonists	W146 (Sanna *et al.*, 2006)	JTE013 (Osada *et al.*, 2002)	–	–	–

The immunomodulator fingolimod (FTY720) may be phosphorylated *in vivo* (Albert *et al.*, 2005) to generate a relatively potent agonist with activity at SIP_1, SIP_3, SIP_4 and SIP_5 receptors (Brinkmann *et al.*, 2002); (Mandala *et al.*, 2002). VPC23019 and VPC44116 have antagonist activity at $S1P_1$ and $S1P_3$ receptors (see Marsolais and Rosen, 2009).

Abbreviations: **AUY954**, an aminocarboxylate analog of fingolimod; **JTE013**, pyrazolopyridine analog; **SEW2871**, 5-(4-phenyl-5-trifluoromethylthiophen-2-yl)-3-(3-trifluoromethylphenyl)-(1,2,4)-oxadiazole; **VPC23019**, (*R*)-phosphoric acid mono-[2-amino-2-(3-octyl-phenylcarbamoyl)-ethyl] ester; **VPC44116**, [3-amino-3-(3-octylphenylcarbamoyl)propyl]-phosphonic acid; **W146**, (*R*)-3-amino-(3-hexylphenylamino)-4-oxobutylphosphonic acid

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