# Sphingosine 1-phosphate enhances excitability of sensory neurons through sphingosine 1-phosphate receptors 1 and/or 3



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**Abstract:**

Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid that has proven to be an important signaling molecule both as an extracellular primary messenger and as an intracellular second messenger. Extracellular S1P acts through a family of five S1P receptors, S1PR1-5, all of which are G protein-coupled receptors associated with different G proteins. Previous work from our laboratory shows that externally applied S1P increases the excitability of small-diameter sensory neurons by enhancing the action potential firing. The increased neuronal excitability is mediated primarily, but not exclusively, through S1PR1. This raises the question as to which other S1PRs mediate the enhanced excitability in sensory neurons. To address this question, the expression of different S1PR subtypes in small-diameter sensory neurons was examined by single-cell quantitative PCR. The results show that sensory neurons express the mRNAs for all five S1PRs, with S1PR1 mRNA level significantly greater than the other subtypes. To investigate the functional contribution of other S1PRs in augmenting excitability, sensory neurons were treated with a pool of three individual siRNAs targeted to S1PR1, R2 and R3. This treatment prevented S1P from augmenting excitability, indicating that S1PR1, R2 and/or R3 are essential in mediating S1P-induced sensitization. To study the role of S1PR2 in S1P-induced sensitization, JTE-013, a selective antagonist at S1PR2, was used. Surprisingly, JTE-013 by itself enhanced neuronal excitability. Alternatively, sensory neurons were pretreated with FTY720, which is an agonist at S1PR1/R3/R4/R5 and presumably downregulates these receptors. FTY720 pretreatment prevented S1P from increasing neuronal excitability, suggesting that S1PR2 does not mediate the S1P-induced sensitization. To test the hypothesis that S1PR1 and R3 mediate S1P-induced sensitization, sensory neurons were pretreated with specific antagonists for S1PR1 and R3, or with siRNAs targeted to S1PR1 and R3. Both treatments blocked the capacity of S1P to enhance neuronal excitability. Therefore my results demonstrate that the enhanced excitability produced by S1P is mediated by S1PR1 and/or S1PR3. Additionally, my results indicate that S1P/S1PR1 elevates neuronal excitability through the activation of mitogen-activated protein kinase kinase. The data from antagonism at S1PR1 to regulate neuronal excitability provides insight into the importance of S1P/S1PR1 axis in modulating pain signal transduction.

**Description:**

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