

S 14-4**THE ATTENUATION OF CELL MOTILITY OBSERVED WITH HIGH DOSES OF SPHINGOSINE 1-PHOSPHATE OR PHOSPHORYLATED FTY720 INVOLVES RGS2 THROUGH ITS INTERACTIONS WITH THE RECEPTOR S1P1**

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Sphingosine 1-phosphate (S1P) stimulation enhances cell motility via the S1P receptor S1P1. We determined that this ligand-induced, receptor-mediated cell motility follows a typical bell-shaped dose response curve, i.e. stimulation with low concentrations of S1P enhances cell motility, whereas excess ligand stimulation suppresses it. So far, the attenuation of the response at higher ligand concentrations has not been explained. We report here that S1P1 interacts with the regulator of G protein signaling (RGS)-2 protein, which is a GTPase-activating protein (GAP) for heterotrimeric G proteins. The RGS2-S1P1 complex dissociated at higher ligand concentrations, yet it was unaffected at low concentrations, suggesting that the dissociated RGS2 is involved in the concurrent inhibition of cell motility. In RGS2 knockdown cells, the inhibition of cell motility induced by high ligand concentrations was rescued. S1P1 internalization was not implicated in the attenuation of the response. Similar results were observed upon stimulation with the phosphorylated form of FTY720 (FTYP), which is an S1P1 agonist. In conclusion, the suppressed response in cell motility induced by excess S1P or FTYP via S1P1 is regulated by RGS2 functioning through a mechanism that is independent of S1P1 internalization.

S 15-1**ROLE OF PREFRONTAL CORTICAL NMDA NR2B SUBTYPE RECEPTOR IN FEAR- AND WORKING-MEMORY**

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Glutamate NMDA receptor (NMDA-R) is required for synaptic plasticity. NMDA-R is composed of NR1, NR2 (A, B, C, and D), and NR3 (A and B) subunits. The formation of a functional NMDA-R requires a combination of NR1, an essential channel-forming subunit, and at least one NR2 subunit. Both NR2A- and NR2B-dependent signaling pathways are involved in long-term synaptic plasticity in the central nervous system. The anterior cingulate cortex (ACC), a part of the prefrontal cortex, is thought to be important for emotional memory, and the medial prefrontal cortex (mPFC), a cortical area anterior to the ACC, is essential for working memory. However, little is known about the functional roles of NR2A and NR2B subunits in the ACC and mPFC in memory functions. In the present study, we provide strong evidence that both NR2A and NR2B subunits in the ACC contribute to the formation of classical contextual fear memory, and NR2B in the mPFC to the behavioral expression and neural representation of working memory.