Fingolimod Ameliorates Central Neuropathic Pain

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19b

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Multiple sclerosis (MS) is an autoimmune-inflammatory neurodegenerative disease that leads to severe neurological and cognitive deficits often accompanied by a debilitating neuropathic pain. Disease-modifying agents slow the progression of MS and prevent relapses, yet it remains unclear which if any of them can also reduce central neuropathic pain. We explored the analgesic potential of fingolimod (FTY720), an agonist/functional antagonist at the sphingosine-1-phosphate receptor 1 (S1PR1) that reduces hyperalgesia in multiple models of peripheral inflammatory or neuropathic pain. We used a myelin oligodendrocyte glycoprotein 35-55 (MOG35-55) mouse model of experimental autoimmune encephalomyelitis (EAE), modified to avoid frank paralysis and thus allow for assessment of withdrawal behaviors to somatosensory stimuli. Daily intraperitoneal fingolimod reduced behavioral signs of central neuropathic pain (mechanical and cold hypersensitivity) in a dose-dependent and reversible manner. Both EAE and fingolimod changed hyperalgesia before modifying motor function, suggesting that pain-related effects and clinical neurological deficits were modulated independently. Fingolimod also reduced cellular markers of central sensitization of neurons in the dorsal horn of the spinal cord: glutamate-evoked Ca2+ signaling and stimulus-evoked phospho- extracellular signal-related kinase ERK (pERK) expression, as well as upregulation of astrocytes (GFAP) and macrophage/microglia (Iba1) immunoreactivity. The antihyperalgesic effects of fingolimod were prevented or reversed by the S1PR1 antagonist W146 (1 mg/kg daily, i.p.), and could be mimicked by either repeated or single injection of the S1PR1-selective agonist SEW2871. We conclude that fingolimod behaves as an S1PR1 agonist rather than as an antagonist to reduce pain in multiple sclerosis by reversing central sensitization of spinal nociceptive neurons.