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FTY720 ameliorates memory and synaptic impairment in the APP/PS1 model of Alzheimer's Disease

Alzheimer's Disease (AD) is the most common cause of dementia. Growing evidence suggests that dysregulation of lipid metabolism, particularly sphingolipid-mediated cellular signaling, is implicated in AD pathogenesis. Sphingosine-1-Phosphate (S1P) is a sphingolipid whose signaling pathway regulates an array of cellular responses, including cell survival and neurogenesis. S1P synthesis decreases as a function of AD progression, and decreased levels of S1P correlate with increased deposition of Amyloid Beta and hyperphosphorylated tau protein in AD brains. Here, we propose to test the hypothesis that S1P administration ameliorates the synaptic and memory deficits of the APP/PS1 amyloidrogenic mouse model of AD. We treated 7-month-old APP/PS1 mice and their WT littermates with FTY720, a drug that enhances S1P signaling and that is FDA-approved for the treatment of multiple sclerosis. Mice received FTY720 through the drinking water at 1 mg/kg/day over two months. After treatment, animals were subjected to hippocampal-dependent Novel Object Recognition (NOR) and Barnes Maze (BM) behavioral tasks, and electrophysiological assessment of CA3-CA1 and EC-EC long-term synaptic plasticity (LTP). We found that FTY720-treated APP/PS1 mice had NOR and BM performance similar to control mice (WT and WT treated with FTY720). Consistently, FTY720-treated APP/PS1 mice showed LTP expression indistinguishable from control mice at the CA3-CA1 and EC-EC synapses. These data indicate that FTY720 treatment can rescue both LTP and memory deficits in amyloidogenic APP/PS1 mice, suggesting that FTY720 (and other S1P modulators) could be a potential drug for AD.