FTY720 (Fingolimod) Attenuates Beta-amyloid Peptide (Aβ_{42})-Induced Impairment of Spatial Learning and Memory in Rats

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Abstract Imbalanced lipid metabolism and increase in the ceramide-to-SIP ratio in the brain have been postulated to play a role in amyloidogenesis, neuroinflammatory reactions, and neuronal apoptosis in Alzheimer’s disease (AD) pathology. FTY720, the immunomodulatory sphingosine 1-phosphate (SIP) analog, has recently gained interest because of its CNS-directed effects. In addition to its immunomodulatory functions in multiple sclerosis, FTY720 possesses anti-inflammatory and neuroprotective roles in different cerebral ischemia models. In the present study, we examined the effects of FTY720 in a rat model of AD. Memory deficit was induced by bilateral intrahippocampus injection of beta-amyloid peptide (Aβ_{42}) and examined through the Morris water maze test. The extent of histological injury in the hippocampus and the activation of caspase-3 were determined respectively by Nissl staining and Western blotting. Chronic daily administration of FTY720 (1 mg/kg, i.p., 14 days) significantly attenuated the Aβ_{42}-induced learning and memory impairment and prevented the hippocampus neuronal damage as well as caspase-3 activation. These data show for the first time that FTY720 has a beneficial effect in restoring memory loss in Aβ_{42}-induced neurotoxicity and also suggest that SIP receptors and signaling pathways may provide a potential target for the treatment of AD.

Keywords FTY720 · Alzheimer’s disease · Sphingosine 1-phosphate · Spatial memory · Neural damage

Introduction

Alzheimer’s disease (AD), the most common age-related neurodegenerative disorder and the most common form of dementia, is a progressive disease, characterized by loss of specific neuronal populations and devastating loss of memory and cognitive function. Although deposition of beta-amyloid (Aβ) peptides, the formation of senile plaques, and the tau protein abnormalities are the core of pathological events in AD, activation of neuroinflammatory reactions and abnormal lipid metabolism in AD brains have gained lots of attention in recent years (Farooqui et al. 2010; Rubio-Perez and Morillas-Ruiz 2012; Bhaskar and Lamb 2012).

The major lipid abnormalities demonstrated in AD brains includes decreases in total phospholipid and sulfatide contents (Han et al. 2002; Farooqui et al. 2010) and increases in ceramide and cholesterol levels (Han et al. 2002; Cutler et al. 2004). Ceramide can be generated within the cells by three main pathways including the de novo synthesis, hydrolysis of the sphingomyelin by the activity of sphingomyelinases, and recycling from sphingosine by the activity of ceramide synthase in the salvage pathway (Tari et al. 2007). It has