Neurorestorative effect of FTY720 in a rat model of Alzheimer's disease: Comparison with Memantine

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HIGHLIGHTS
• Protective effect of FTY720, the SIP analog, is compared to Memantine in AD rats.
• FTY720 as well as Memantine restores memory in male and female AD rats.
• FTY720 as well as Memantine prevents from hippocampal neuron loss in AD rats.
• FTY720 as well as Memantine alters gene transcript profile toward neuroprotection.

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ABSTRACT
Alzheimer’s disease (AD) as a neurodegenerative brain disorder is the most common cause of dementia. To date, there is no causative treatment for AD and there are few preventive treatments either. The sphingosine-1-phosphate receptor modulator FTY720 ( fingolimod) prevents lymphocytes from contributing to an autoimmune reaction and has been approved for multiple sclerosis treatment. In concert with other studies showing the anti-inflammatory and protective effect of FTY720 in some neurodegenerative disorders like ischemia, we have recently shown that FTY720 chronic administration prevents from impairment of spatial learning and memory in AD rats. Here FTY720 was examined on AD rats in comparison to the only clinically approved NMDA receptor antagonist, Memantine. Passive avoidance task showed significant memory restoration in AD animals received FTY720 comparable to Memantine. Upon gene profiling by QuantiGene PLEX, this behavioral outcomes was concurrent with considerable alterations in some genes transcripts like that of mitogen activated protein kinases (MAPKs) and some inflammatory markers that may particularly account for the detected decline in hippocampal neural damage or memory impairment associated with AD. From a therapeutic standpoint, our findings conclude that FTY720 may suggest new opportunities for AD management probably based on several modulatory effects on genes involved in cell death or survival.

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1. Introduction
To date, established treatments for Alzheimer's disease (AD) include cholinesterase inhibitors [1] and Memantine that is an uncompetitive, moderate-affinity N-methyl-D-aspartate (NMDA) receptors antagonist [2]. Memantine is believed to protect neurons from excitotoxicity, as a major contributing mechanism to escalating dementia [3]. According to systemic clinical studies on AD patients, Memantine improves cognition [4] and may reduce behavioral and psychological symptoms of dementia [5]. In spite of the promising results however, Memantine treatment as other currently available ones for AD (Donepezil, Rivastigmine and Galantamine) is symptomatic and does not halt the disease progression [6], the fact necessitates new drug investigations upon comprehensive knowledge of AD and accompanying dementia.

AD is highly associated with deregulation of lysophospholipids (LPS) of which one of the best known is sphingosine-1-phosphate (SIP) [7]. LPS can play multiple roles in relevance to CNS disorders, especially those associated with CNS injuries and inflammation,