

problems with balance and coordination. Brain tissues are currently undergoing analyses to determine whether DFO affected inflammation and insulin receptor signaling. These results further support the potential of IN DFO for use as a treatment for Alzheimer's disease.

P2-314 **NSX-0527: A NOVEL M1/M4-SELECTIVE MUSCARINIC AGONIST FOR ALZHEIMER'S DISEASE**

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Background: The selective activation of M1 muscarinic receptors has great potential to treat both the symptomatic and pathological aspects of Alzheimer's disease. Implementation of this strategy has been challenging, since potent compounds are likely to produce intolerable side effects. The compound NSX-0527 robustly activates the M1 receptor and yields side effects that are easily controlled. **Methods:** In vitro M1 and M3 activation was measured using the IP-One Terbium HTRF assay kit. In vitro human liver metabolism of drugs was determined by LC/MS/MS. In vivo M1 activation was evaluated using a newly developed IP1 assay, and cognitive benefit was measured using the novel object recognition assay. Hippocampal ABeta1-42 levels were monitored using microdialysis and ELISA. **Results:** NSX-0527 selectively activated human M1 muscarinic receptors in vitro at 81% of the maximal carbachol response. The compound was sparsely metabolized by human liver microsomes compared with a similar drug (xanomeline), yielding a predicted half-life of 5.8-7.2 hrs. NSX-0527 and its closely related analogue NSX-0559 potently increased hippocampal IP1 levels, especially compared with xanomeline and talsacladine. Mice dosed with NSX-0527 displayed heightened interest in a novel object one hour after PBS-dosed mice evidenced natural forgetting in the same assay. Treatment with NSX-0527 in Tg2576 mice reduced ABeta1-42 levels by 50% at a dose of 15 mg/kg. Formulations of NSX-0527 and NSX-0559 effectively eliminated the salivation side effect response seen in rats at high doses. **Conclusions:** NSX-0527 potently and selectively activates the M1 muscarinic pathway, making it a promising treatment for Alzheimer's disease.

P2-315 **PRESERVATION OF SYNAPTIC PLASTICITY AND NEURONAL INTEGRITY IN A MOUSE MODEL OF ALZHEIMER'S DISEASE**

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Background: Synaptic alteration/dysfunction is increasingly viewed as one of the earliest events in the initiation of AD-type cognitive decline. The onset of cognitive decline correlates better with synaptic dysfunctions than with hallmark pathologies such as extracellular amyloid- β (A β) plaques, intracellular hyperphosphorylated tau or neuronal loss. Numerous studies have demonstrated significant alterations in the structure of dendrites and spines both in AD and in mouse models of AD, including dystrophic dendrites, aberrant sprouting, curvature of dendritic processes, and loss of

dendritic spines with accompanying synapse loss in hippocampal and neocortical pyramidal cells. The loss of synapses and dendritic spines also correlates with increased levels of soluble A β both in human postmortem brains and in transgenic mouse models of AD. Most importantly, synaptic loss shows the most robust correlation with cognitive decline in AD. Therefore, preventing synapse loss and restoring synaptic function may provide a viable strategy for early protection/intervention to slow AD progression and preserve cognitive function. **Methods:** Electrophysiology is used to record LTP; confocal laser scanning microscope and the high-resolution automated 3D reconstruction system are used to study dendritic structure. **Results:** Polyphenols are receiving increasing attention for their potential role in preventing the onset and/or progression of preclinical AD into frank AD dementia. Our lab has identified and characterized a set of brain-bioavailable polyphenol metabolites with drug-like properties that can significantly preserve synaptic plasticity and neuronal structure in the context AD. Specifically, we found that 3'-O-methyl-epicatechin-5-O- β -glucuronide (Me-EC-Glur), cyanidin-3'-O-glucoside and quercetin-3'-O-glucuronide, are capable of preventing oligomeric A β -mediated LTP dysfunction through the activation of cAMP response element-binding protein (CREB) signaling pathways. Moreover, we found that Me-EC-Glur is able to restore neuronal structure including increasing the total length of dendrites and increasing dendritic complexity in primary neurons derived from Tg2576 mice, through mechanisms associated with cofilin-mediated F-actin disassembly and dendritic/synaptic growth. The preclinical efficacy of these polyphenol compounds are currently being investigated in Tg2576 mice, which has demonstrated synaptic dysfunction and cognitive impairments during aging. **Conclusions:** Our study will lead to the immediate translational application of novel therapeutic agents to preserve cognitive function and prevent, or at least delay, the onset and progression of AD.

P2-316 **REMYELINATION IMPROVES MEMORY IMPAIRMENT IN THE EARLY STAGE OF AN ALZHEIMER'S DISEASE TRANSGENIC MOUSE MODEL**

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Background: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder with behavioral and cognitive impairments. The classical hypotheses such as amyloid hypothesis and tau hypothesis have been questioned and attributed little to effective treatment. Other hypotheses were gradually appearing for exploring AD and guide the treatment, including "myelin retrogenesis" proposed by Bartzokis et al in 2004. The aim of the present study was to explore the relationship of myelin impairments and cognitive impairments, and whether remyelination could be done with anti-LINGO-1 intervention at the early stage of 5XFAD mice. **Methods:** The LINGO-1 antibody was administered at the end of 1st month old mice. 1st and 3rd month old 5XFAD mice and controls were detected the memory change by Morris water maze, scanned by micro MRI (T2 and DTI) to observe the brain structure, followed by collection of brain tissues for electron microscopy and Western blot. **Results:** The percentage of the time spent on the quadrant and the crossovers