Control/Tracking Number: 2014-S-14316-SfN
Activity: Scientific Abstract
Current Date/Time: 5/11/2014 8:45:22 PM

The novel M1/M4-selective muscarinic agonist NSX-0527 for the treatment of Alzheimer's disease

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Abstract:
Selective M1 muscarinic agonists have long held promise as potential treatments for Alzheimer's disease (AD). However, compounds investigated in early clinical trials suffered from a lack of efficacy, likely due to low potency. The M1/M4-preferring agonist xanomeline, a more recent compound that has undergone significant clinical assessment, did show efficacy in AD patients in a Phase II trial, but was abandoned due to poor tolerability. NSX-0527 is an M1/M4-selective orthosteric muscarinic agonist showing good bioavailability (~75%) and brain penetration (~60%). It has excellent metabolic stability as determined by incubation in human liver microsomes. A half-life of approximately one hour was measured in rats. NSX-0527 displayed potent activation of central M1 receptors as demonstrated by an increase in hippocampal inositol-1-phosphate (IP1) concentration following oral dosing in rats with significantly greater intrinsic efficacy and potency compared to xanomeline. In the novel object recognition behavioral test, mice receiving subcutaneous doses of NSX-0527 as low as 0.1 mg/kg showed improved cognitive performance compared to controls. Finally, NSX-0527 produced an acute reduction of hippocampal A-Beta1-42 in Tg2576 transgenic mice as measured by microdialysis, indicating the potential of NSX-0527 for disease-modifying activity in Alzheimer's disease.
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Presentation Preference (Complete): Poster Only
Linking Group (Complete): None selected
Nanosymposium Information (Complete):
Theme and Topic (Complete): C.19.b. Neurodegenerative diseases (AD, PD, MS, stroke) ; C.02.k. Alzheimer's disease: In vivo approaches in animals
Keyword (Complete): MUSCARINIC ; ALZHEIMER'S ; DRUG
Support (Complete):
Support: No

Special Requests (Complete):