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Neuroscience 2015

Presentation Abstract

Program#/Poster#:	502.10/J38
Presentation Title:	NSX-0527: A novel M1/M4 selective muscarinic agonist with antipsychotic and cognition-enhancing properties
Location:	Hall A
Presentation time:	Tuesday, Oct 20, 2015, 8:00 AM -12:00 PM
Presenter at Poster:	Tue, Oct. 20, 2015, 9:00 AM - 10:00 AM
Topic:	++C.15.h. Experimental therapeutics
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Abstract:	Schizophrenia affects nearly 2.5 million Americans, comprising 1.1% of the adult population. Many treatments are approved, but pharmacotherapy of the disease remains problematic. Antipsychotics do provide some benefit in mitigating the positive symptoms of the disease (delusions and hallucinations), but have little effect on the negative symptoms (emotional blunting) and cognitive symptoms (impaired learning and memory). However, these compounds produce drowsiness, weight gain, and metabolic disruption, which can lead to significant morbidity and contribute to decreased medication adherence. Research into muscarinic agonists has suggested that pharmacologically balancing dopaminergic and cholinergic activity via stimulation of M4 muscarinic receptors may be as effective in treating schizophrenia as currently approved therapies. Several muscarinic agonists have been investigated in early clinical trials with the target indication of Alzheimer's disease. One of these, the M1/M4-preferring agonist xanomeline showed efficacy in AD patients. Interestingly, in addition to cognitive benefits, the compound reduced vocal outbursts, suspiciousness, delusions, agitation, and hallucinations. NSX-0527 is an M1/M4-selective orthosteric muscarinic agonist showing good bioavailability (~75%) and brain penetration (~60%), excellent metabolic stability, and a half-life of approximately one hour in rats. It was investigated in three behavioral antipsychotic assays: reversal of apomorphine-induced climbing, reversal of MK-801- and amphetamine-induced hyperlocomotion, and inhibition of conditioned avoidance response. NSX-0527 compared favorably to xanomeline as well as olanzapine without producing the classic antipsychotic side effect of hyperprolactinemia. NeuroSolis has also developed an NSX-0527 formulation that minimizes the peripheral effects of high doses. Finally, mice dosed with NSX-0527 demonstrated

improved memory in the novel object recognition test, suggesting that NSX-0527 has the potential to be a first-in-class treatment that both reduces positive symptoms and enhances cognition.

Disclosures: **J.C. Ockuly:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis, Inc. **J.D. Beck:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis Inc. **S.A. Hanson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis Inc. **M.L. Hendrickson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis Inc..

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