Targeting lncRNA NEAT1 Impedes Alzheimer's Disease Progression via MicroRNA-193a Mediated CREB/BDNF and NRF2/NQO1 Pathways

Yuanlong Li, MD

Department of Pharmacy, Henan Provincial People's Hospital, Zhengzhou, Henan, China

Abstract

Background. Long noncoding RNA nuclear-enriched abundant transcript 1 (lnc-NEAT1) is closely implicated in neurological or degenerative diseases, while its implication in AD is rarely reported. This study aimed to investigate the effect of lnc-NEAT1 knockdown on neuron injury, inflammation, and oxidative stress in AD, as well as its interaction with downstream targets and pathways.

Methods. APPswe/PS1dE9 transgenic mice were injected with negative control or lnc-NEAT1 interference lentivirus. Besides, AD cellular model was constructed by amyloid β treatment in mice primary neuron cells; then, knockdown of lnc-NEAT1 and microRNA-193a (miR-193a) was performed alone or in combination.

Results. *In vivo* experiments revealed that Lnc-NEAT1 knockdown improved cognition in AD mice reflected by Morrison water maze and Y-maze assays. Besides, lnc-NEAT1 knockdown reduced injury and apoptosis, decreased TNF-α and IL-1β levels (indicating lower inflammation level), repressed ROS, MDA but promoted ATP and SOD levels (suggesting lower oxidative stress level), and activated CREB/BDNF and NRF2/NQO1 pathways in hippocampi of AD mice. Notably, lnc-NEAT1 down-regulated miR-193a both *in vitro* and *in vivo;* also, it acted as a decoy of miR-193a. *In vitro* experiments showed that lnc-NEAT1 knockdown decreased apoptosis and oxidative stress, improved cell viability, and also activated CREB/BDNF and NRF2/NQO1 pathways in AD cellular model. Meanwhile, miR-193a knockdown showed the opposite effects, which also attenuated lnc-NEAT1 knockdown-mediated reduction in injury, oxidative stress, and activation of CREB/BDNF and NRF2/NQO1 pathways of AD cellular model.

Conclusion. Lnc-NEAT1 knockdown reduces neuron injury, inflammation, and oxidative stress through activating miR-193a mediated CREB/BDNF and NRF2/NQO1 pathways in AD.

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Impact of AXS-05 (DEXTROMETHORPHAN-BUPROPION), an Oral NMDA Receptor Antagonist, on Anhedonic Symptoms in Major Depressive Disorder

Amanda Jones, PharmD[1], Roger S. McIntyre, MD[2], Mark Jacobsen[1], Caroline Streicher[1], Zachariah Thomas, PharmD, MPH[1] and Herriot Tabuteau, MD[1]

[1]Axsome Therapeutics, NY and [2]University of Toronto and the Brain and Cognition Discovery Foundation, Toronto, Canada

Abstract

Background. Treatments for MDD that can improve both overall depressive and anhedonic symptoms are urgently needed.

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity being developed for MDD. The dextromethorphan component of AXS-05 is an NMDA receptor antagonist and a sigma-1 receptor agonist. The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan.

Objective. To evaluate the effect of AXS-05 in improving anhedonic symptoms in MDD.

Methods. GEMINI (N=327) was a randomized, double-blind, placebo-controlled, 6-week study, which randomized adults with MDD to AXS-05 (dextromethorphan HBr 45 mg- bupropion HCl 105 mg) or placebo, twice daily. The primary endpoint was change from baseline in the MADRS total score at Week 6. A post-hoc analysis was conducted to determine the impact of AXS-05 versus placebo on the 5-item MADRS anhedonia subscale (MAS).

Results. Baseline MAS scores were 19.8 and 19.6 in the AXS-05 and placebo group, respectively. At Week 1, AXS-05 treatment resulted in a significant mean reduction from baseline in the MAS score of 4.44 versus 2.69 points for placebo ($p< 0.001$). At Week 6, the mean reduction from baseline in the MAS was 9.70 for AXS-05 compared to 7.22 for placebo ($p=0.001$). Response rates ($\geq$ 50% MAS improvement) were significantly greater for AXS-05 compared to placebo at Week 1 ($p< 0.001$) and at every time point thereafter.

Treatment with AXS-05 was generally safe and well tolerated. The most common adverse events being dizziness, nausea, headache, diarrhea, somnolence, and dry mouth.

Conclusions. Treatment with AXS-05 rapidly and significantly reduced anhedonic symptoms as well as overall depressive symptoms.

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