Effect of the Neurogenic Molecule NSI-189 on indices of cognition in an APP/Tau mouse model of Alzheimer's disease.

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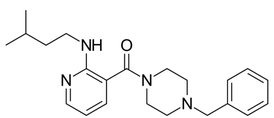
Background

Alzheimer's disease (AD) neurodegeneration and synaptic dysfunction affect the cortex and the limbic system, along with Aβ deposits and neurofibrillary tangles, leading to cognitive deficits (Terry et al., 1991).

Neuropsychiatric disorders are additional features of AD (Lanctot et al., 2017) and depression is a risk factor for the development of AD and significantly increase the conversion of Mild Cognitive Impairments (MCI) to AD

NSI-189: benzylpiperizine-aminopyridine, orally active, stimulates neurogenesis, synaptogenesis and increased hippocampal volume in mice.



NSI-189 was shown to have significant antidepressant and pro-cognitive effects in patients with major depressive disorder in a Phase II clinical trial

Material and Methods

Animals: Transgenic TAPP mice carry transgenes for human APP(Swe) and human tau (P301L) to model familial AD with Aβ deposition, NFTs and neurodegeneration.

18 weeks old mice (**when memory deficits are first detected)** were treated orally for 12 weeks with NSI-189 at 30 mg/kg.

After 6 and 12 weeks of treatment, learning and memory tests (Barnes maze and Object recognition tests) were performed along repeated testing on the rotarod for assessing motor learning.

At termination, brains were collected and hippocampus homogenized and submiited to Western blotting for the neuronal marker (NeuN)

Results

Figure 1: Improvement of learning abilities

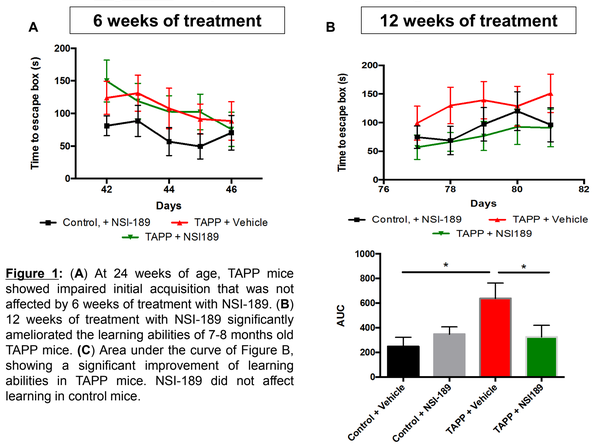
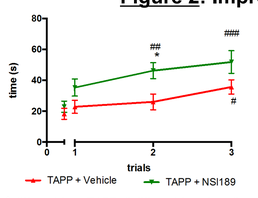


Figure 1: (**A**) At 24 weeks of age, TAPP mice showed impaired initial acquisition that was not affected by 6 weeks of treatment with NSI-189. (**B**) 12 weeks of treatment with NSI-189 significantly ameliorated the learning abilities of 7-8 months old TAPP mice. (**C**) Area under the curve of Figure B, showing a significant improvement of learning abilities in TAPP mice. NSI-189 did not affect learning in control mice.

Figure 2: Improvement of motor learning.



* different from TAPP, # different from baseline

Figure 2: Rotarod performances were decreased in TAPP mice receiving vehicle. The motor performance as well as the learning ability of TAPP mice receiving daily NSI-189 treatment were significantly improved compared to TAPP.

Results

Figure 3: Improved short- and Long-term memory

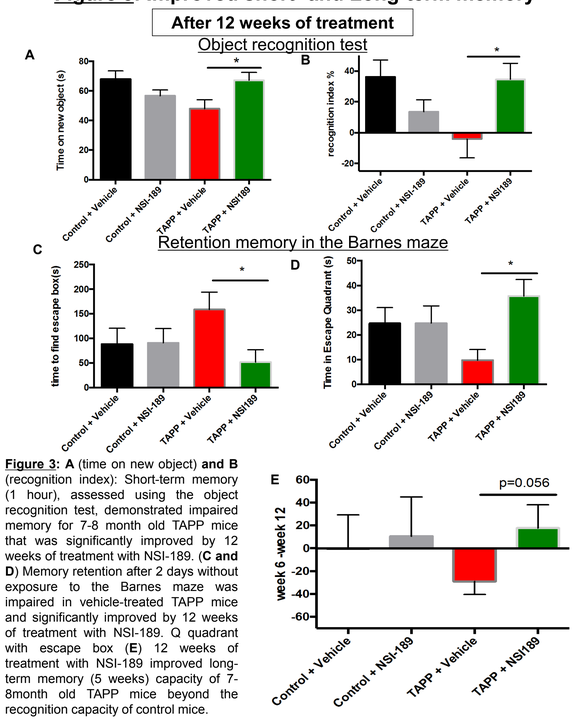


Figure 3: A (time on new object) **and B** (recognition index): Short-term memory (1 hour), assessed using the object recognition test, demonstrated impaired memory for 7-8 month old TAPP mice that was significantly improved by 12 weeks of treatment with NSI-189. (**C and D**) Memory retention after 2 days without exposure to the Barnes maze was impaired in vehicle-treated TAPP mice and significantly improved by 12 weeks of treatment with NSI-189. Q quadrant with escape box (**E**) 12 weeks of treatment with NSI-189 improved long-term memory (5 weeks) capacity of 7-8month old TAPP mice beyond the recognition capacity of control mice.

Results

Figure 4: Partial neuroprotection

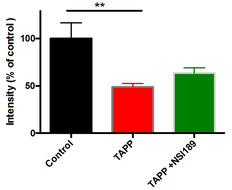


Figure 4: Neuronal loss
The neuronal nuclear protein NeuN was significantly reduced in the hippocampus of 7-8 months old TAPP mice and was partially prevented by treatment with NSI-189.

All data expressed as mean±sem, n=14-15, *p<0.05, **, p<0.001, p<0.001, one-way ANOVA followed by Dunnetts post hoc test vs TAPP+ Vehicle group.

Summary

- Learning abilities were significantly ameliorated by 12 weeks of oral administration of NSI-189.
- 12 weeks of treatment with NSI-189, significantly restored short and long-term memory retention in the Barnes maze
- Thirteen weeks of treatment with NSI-189 improved short-term memory capacity of 7-8 month old TAPP mice in the novel object recognition test.
- Using the repeated rotarod test showed that the motor performance as well as the learning ability of TAPP mice receiving daily NSI-189 treatment were significantly improved.
- Neuronal loss in TAPP hippocampus was partially prevented by 12 weeks of treatment with NSI-189.

treatment with NSI-189 in an interventional paradigm improved learning and memory behaviors in a mouse model of AD, carrying both human APP and human tau genes.