Effect of Neurogenic Compound NSI-189 on indices of cognition and Anxiety in a mouse model (5xFAD) of Alzheimer's disease.

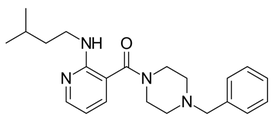
Corinne G Jolivalt, Ph.D.[1] , Alexandra Marquez[1] , David M Quach[2] and Karl K Johe, Ph.D.[2] ,
(1)University of California San Diego, San Diego, CA, USA, (2)Neuralstem, Inc., Germantown, MD, USA

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

Materials and Methods

Animals: Transgenic 5xFAD mice carry transgenes for mutant human APP and mutant human PS1 to model familial AD with early Aβ deposition and neurodegeneration.

15 weeks old mice (**when memory deficits are first detected** (Oalkley et al., 2006) 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 with anxiety test and 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

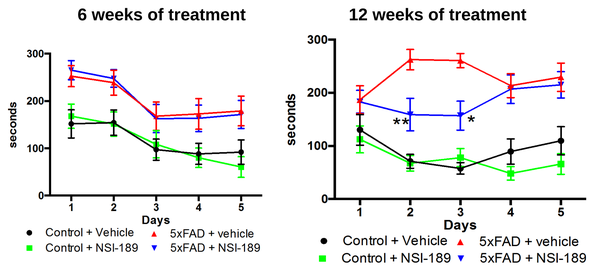
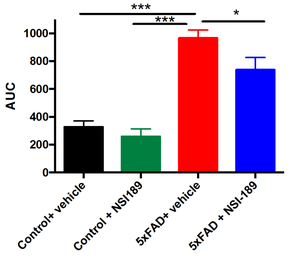


Figure 1: Learning abilities in the Barnes Maze. (**A**) At 21 weeks of age, 5xFAD mice showed impaired initial acquisition that was not affected by 6 weeks of treatment with NSI-189. (**B**) 12 weeks of treatment with NSI-189 significantly ameliorated the learning abilities of 7 months old 5xFAD mice. (**C**) Area under the curve of figure B, showing a significant improvement of learning abilities in 5xFAD mice. NSI-189 did not affect learning in control mice.



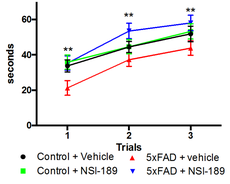


Figure 2: Motor learning.
Rotarod performances were decreased in 5xFAD mice receiving vehicle. The motor performance as well as the learning ability of 5xFAD mice receiving daily NSI-189 treatment were significantly improved compared to 5xFAD mice above control mice values

Results

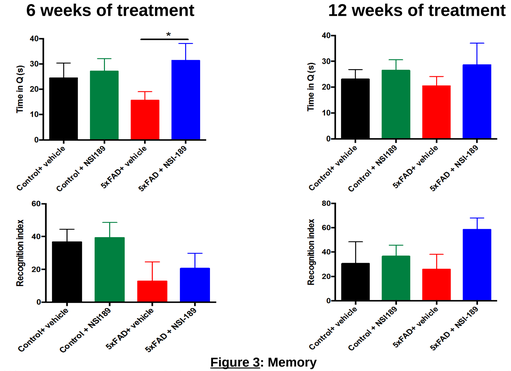


Figure 3: Memory
(**A**) Memory retention after 2 days without exposure to the Barnes maze was impaired in vehicle-treated 5xFAD mice and significantly improved by 6 weeks of treatment with NSI-189 in 5xFAD mice. (**B**) Amelioration of memory retention was also noted after 12 weeks of treatment but it did not reach significance. (**C**) Short-term memory (1 hour), assessed using the object recognition test, demonstrated impaired memory for 5month old 5xFAD mice and 6 weeks of treatment with NSI-189 marginally attenuated the memory impairment. (**D**) 12 weeks of treatment with NSI-189 improved memory capacity of 7month old 5xFAD mice beyond the recognition capacity of control mice

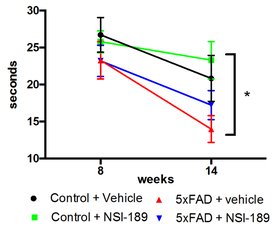


Figure 4: Anxiety assessment
At 5 months of age (8 weeks time point), control and 5xFAD mice spent similar time on the edges but 5xFAD mice tend to be more anxious. 6 weeks treatment with NSI-189 did not affect control or 5xFAD mice behavior. At 7 months of age (14 weeks time point), anxiety levels have increased for control and 5xFAD mice. 6 additional weeks of treatment with NSI-189, partially reduced the developing anxiety in 5xFAD mice. This effect was also noted for control mice.

Results

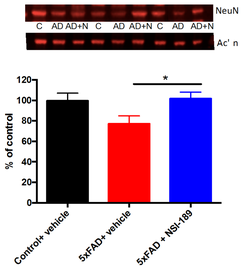


Figure 5: Neuronal loss
The neuronal nuclear protein NeuN was significantly reduced in the hippocampus of 7 months old 5xFAD mice and was significantly prevented by treatment with NSI-189.

All data expressed as mean±sem, n=14-15, *p<0.05, **, p<0.001, p<0.001, reapet measures ANOVA followed by,Tukey post hoc test or one-way ANOVA followed by Dunnetts post hoc test vs 5xFAD+ Vehicle group.

Summary

- 6 weeks of treatment with NSI-189, significantly restored memory retention in the Barnes maze
- Learning abilities were significantly ameliorated by 12 weeks of oral administration of NSI-189.
- Thirteen weeks of treatment with NSI-189 improved short-term memory capacity of 7month old 5xFAD mice beyond the recognition capacity of control mice in the novel object recognition test.
- Using the repeated rotarod test showed that the motor performance as well as the learning ability of 5xFAD mice receiving daily NSI-189 treatment were significantly improved in 5xFAD.
- Anxiety had increased over the study period for untreated mice but daily treatment with NSI-189 partially reduced the developing anxiety for both control and AD mice.

Daily treatment with NSI-189 in an interventional paradigm improved learning and memory behaviors as well as reduced developing anxiety in a mouse model of AD.