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

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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.

Summary

- 6 weeks of treatment with NSI-189, significantly restored memory retention in the Barnes maze.
- Learning abilities were significantly ameliorated after 12 weeks of oral administration of NSI-189.
- Thirteen weeks of treatment with NSI-189 improved short-term memory capacity of 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 compared to control mice.
- 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.

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 synaptic dysfunction affecting 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 was shown to have significant antidepressant and pre-cognitive effects in patients with major depressive disorder in a Phase II clinical trial.

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

- 15 weeks old mice (when memory deficits are first detected (Oakley 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 submitted to Western blotting for the neuronal marker (NeuN).

- 5xFAD mice. NSI-189 did not affect learning in control mice. Significant improvement of learning abilities in 5xFAD mice receiving daily NSI-189 treatment were noted after 12 weeks of treatment but it did not reach significance.

- At 5 months of age (8 weeks time point), anxiety was significantly improved in 5xFAD. Thirteen weeks of treatment with NSI-189 partially reduced the developing anxiety for both control mice and 5xFAD mice and was significantly prevented by treatment with NSI-189.

Results

- At termination, brains were collected and hippocampus homogenized and submitted to Western blotting for the neuronal marker (NeuN). - 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 compared to control mice. - 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.

Figure 1: Learning abilities in the Barnes Maze

<table>
<thead>
<tr>
<th>Time</th>
<th>Control + Vehicle</th>
<th>NSI-189 + vehicle</th>
<th>NSI-189 + SAfAD</th>
<th>NSI-189 + SAfAD + Vehicle</th>
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<tbody>
<tr>
<td>6 weeks of treatment</td>
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<td>12 weeks of treatment</td>
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Figure 2: Memory

- Memory retention after 2 days without exposure to the Barnes maze was impaired in 5xFAD mice and significantly improved by 6 weeks of treatment with NSI-189. (A) Area under the curve of figure B, showing a significant improvement of learning abilities in 5xFAD mice receiving daily NSI-189 did not affect learning in control mice.

Figure 3: Anxiety assessment

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All data expressed as mean ± SEM, n=14-15, *p<0.05, **p<0.001, ***p<0.001, repeated measures ANOVA followed by Tukey post hoc test or one-way ANOVA followed by Duncan post hoc test as indicated in the figure.