The mitochondrial targeted drug SBT-272 attenuates dopaminergic neuron loss, alpha-synuclein burden and neuroinflammation in a mouse model of Parkinson’s Disease

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ABSTRACT

Objective—To assess the preclinical efficacy of the investigational drug SBT-272 in a mouse model of Parkinson’s disease (PD).

Background—SBT-272 is a peptidomimetic drug that targets the mitochondrial inner membrane through interactions with the mitochondrial cardiolipin and is in phase I clinical trials. SBT-272 stabilizes mitochondrial inner membrane structure under conditions of stress, preventing the generation of reactive oxygen species (ROS) and maintaining mitochondrial bioenergetics. Mitochondrial dysfunction has been described as a downstream consequence of alpha-synuclein toxicity in neurons; therefore, we have investigated the ability of SBT-272 to prevent neurodegeneration in a mouse model of PD induced by viral expression of mutant alpha-synuclein.

Methods—SBT-272 was delivered via subcutaneous or intraperitoneal injection. Cerebral ischemia in rats was induced by middle cerebral artery occlusion, and mitochondrial respiration was assessed in brain homogenates by high resolution respirometry. C57BL/6 mice were transduced with AAV5 expressing mutant human A53T alpha-synuclein to model PD. Dopaminergic neurons were identified with tyrosine hydroxylase immunostaining, and cell counts in the substantia nigra pars compacta were performed via automated stereology. Alpha-synuclein aggregates quantified via immunostaining. Neuroinflammation was assessed via immunostaining for activated microglial cells (Iba-1) and astrocytes (GFAP).

Results—Systemic SBT-272 crosses the BBB and is pharmacologically active in a brain model of ischemic stroke. In a mouse model of PD, aggregated alpha-synuclein levels were significantly decreased (figure 2), leading to reduced loss of dopaminergic neurons in the substantia nigra pars compacta (figure 3) following SBT-272 treatment. A dose responsive reduction of neuroinflammation was also observed (figure 4).

Conclusion—SBT-272 prevented the loss of dopaminergic neurons, decreased alpha-synuclein burden and attenuated neuroinflammation in the substantia nigra following mutant alpha-synuclein induced toxicity in mice. These data support further investigation of SBT-272 in PD.

INTRODUCTION

- Parkinson’s disease (PD) is a progressive multi-system neurodegenerative disease that primarily affects patients later in life.
- PD is the second most common neurodegenerative disease in the world, with a reported prevalence in industrialized countries around 0.3% of the entire population and about 1% in people > 60 years of age.
- PD prevalence increases with advancing age in men and women.
- PD has distinctive neuropathological brain changes including the appearance of abnormal proteinaceous spherical bodies (Lewy bodies), and spindle-or thread-like branching Lewy neurites in the somata of the involved nerve cells.

BACKGROUND

- Mutant alpha-synuclein is a protein associated with neurodegenerative diseases such as Parkinson’s disease.
- Misfolded, or mutant alpha-synuclein, is therefore considered to be a potential drug target in PD.
- Mitochondrial dysfunction is known to be involved in the pathogenesis of PD, and includes altered mitochondrial bioenergetics and generation of toxic levels of reactive oxygen species (ROS) that contribute to inflammatory cascades.
- The mitochondrial phospholipid cardiolipin influences alpha-synuclein aggregation, and aberrant cardiolipin has been observed in numerous PD models.

SBT-272

- SBT-272 is a peptidomimetic drug that targets the mitochondrial inner membrane and interacts with cardiolipin to stabilize mitochondrial structure and function.
- SBT-272 is currently in Phase I clinical trials and has been rationally designed as a more CNS-penetrant version of elamipretide, a late-stage compound in development for ophthalmic, neuromuscular, and cardiomyopathic indications.

METHODS

- 9 week-old C57BL/6 mice were bilaterally injected with 1.5 μL of AAV5-hSNCAIIS3A at a concentration of 4 X 10E10 vg/ml into the substantia nigra pars compacta according to the following coordinates: AP = -2.9/ L = ±1.2, DV = ±4.4 from skull. The animals were then sacrificed after 5 weeks, the brains were collected and subjected to different procedures based on the type of analysis. AAV9-mock injected animals were used as controls.
- SBT-272 was daily administered by intraperitoneal injection to C57Bl/6 mice at two different doses (0.5 and 5 mg/kg/day).
- Cerebral ischemia was induced in rats by middle cerebral artery occlusion.
- Mitochondrial respiration was assessed in brain homogenates by high resolution respirometry.
- Dopaminergic neurons were identified with tyrosine hydroxylase immunostaining, and cell counts in the substantia nigra pars compacta were performed via automated stereology.
- Alpha-synuclein aggregation was quantified via immunostaining.
- Neuroinflammation was assessed via immunostaining for activated microglial cells (IBA-1) and astrocytes (GFAP).

RESULTS

- Figure 1: Systemic administration of SBT-272 crossed the blood-brain barrier (BBB) and showed pharmacological activity in an experimental model of ischemic stroke. In these studies, SBT-272 treatment led to a significant improvement in brain mitochondrial function, as assessed by the respiratory control ratio.
- Figure 2: In the PD model, alpha-synuclein aggregation was significantly elevated in the substantia nigra pars compacta. This elevation was attenuated with SBT-272. ***, P<0.001 versus saline.
- Figure 3: Loss of dopaminergic neurons in the substantia nigra pars compacta was mitigated with SBT-272. ***, P<0.001 versus saline.
- Figure 4: The increased neuroinflammation in the PD model was decreased in a dose-dependent manner with SBT-272 as assessed by microglial cells (left) or astrocytes (right). * P<0.05 versus saline.

CONCLUSIONS

- The administration of SBT-272 to C57Bl/6 mice with modeled PD prevented the loss of dopaminergic neurons.
- SBT-272 decreased alpha-synuclein burden and attenuated neuroinflammation in the substantia nigra following mutant alpha-synuclein.
- These data highlight the potential of SBT-272 as a potential therapeutic for treating neurodegenerative diseases.

References

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