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Aldose Reductase Inhibitor AT-007 Prevents Mitochondrial Dysfunction And Neurodegeneration In Sorbitol Dehydrogenase Deficiency-Induced Neuropathy

Abstract: Sorbitol dehydrogenase (SORD) deficiency has been identified as the most frequent autosomal recessive form of hereditary neuropathy, affecting roughly 10,000 patients worldwide. Loss of SORD causes high sorbitol levels in cells due to the inability to convert sorbitol to fructose in the two-step polyol pathway, leading to neurodegeneration. However, underlying mechanisms of sorbitol-induced neurodegeneration have not been fully elucidated. A Drosophila model of SORD deficiency was characterized by locomotor assay and brain imaging. Reactive oxygen species (ROS) staining in the brain, ventral nerve cord, and muscle, as well as patient fibroblasts was performed to understand the pathological changes at the molecular level. To reduce sorbitol accumulation by inhibiting conversion from glucose, a next-generation central nervous system (CNS) penetrant aldose reductase inhibitor (ARI) developed by Applied Therapeutics, Inc, named AT-007, was applied to patient fibroblasts, patient-derived motor neurons, and flies. Sorbitol levels in cells and fly brains were measured, and neurological phenotypes of flies were analyzed.

We showed progressive synaptic degeneration in the fly brain, revealed with lamina vacuoles and electroretinogram abnormalities. In addition, with a novel automated behavior geotaxis monitoring system, we showed a locomotor impairment in SORD deficiency flies, due to abnormal neuromuscular junction innervation in the leg. Finally, we found an accumulation of ROS in the CNS and muscle of the flies, as well as patient fibroblasts, indicating mitochondrial dysfunction. AT-007 significantly reduced sorbitol levels in patient fibroblasts, patient-derived motor neurons, and the Drosophila model. Moreover, we demonstrated that feeding with AT-007 in Drosophila significantly improved locomotor activity, mitigated synaptic degeneration, and reduced ROS levels. Our findings establish the underlying disease pathogenesis and provide a potential treatment strategy for patients with SORD deficiency.

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Biography: Amanda is a native of Florida with roots deeply embedded in Brazilian heritage. Amanda's earlier years were marked by a blend of living in Brazil and returning to the US to complete her education. She embarked on her journey to obtain an Associate's degree at Broward College, followed by her Bachelor's degree in Biology at St. Thomas University. In 2019 she was admitted into the Human Genetics and Genomics graduate program at the University of Miami, where she completed her PhD this past February. It was there that she found her mentor, Dr. Grace Zhai, whose research seamlessly aligned with Amanda's interests in human genetics and neurodegeneration. Amanda sought collaborations, leaving her mark with scholarly contributions of three first author papers and four middle author papers, as well as attending and presenting at national and international conferences. Now, as a postdoctoral scholar at the University of Chicago, Amanda aims to continue paving the way for potential interventions using therapeutic approaches for other genetic neurological disorders. In her spare time, Amanda enjoys playing soccer, going to the beach, or adventurous traveling.

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