PERIPHERAL NERVE SOCIETY
2022 ANNUAL MEETING
14-17 MAY INTERCONTINENTAL MIAMI
MIAMI

Aldose reductase inhibitor AT-007 alleviates mitochondrial dysfunction and neurodegeneration in sorbitol dehydrogenase deficiency-induced neuropathy

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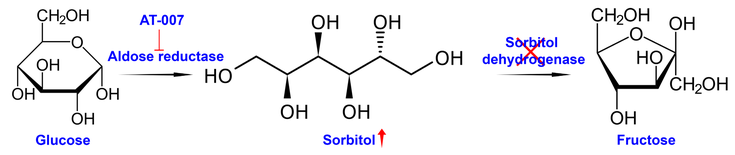
APPLIED THERAPEUTICS

UFL4 University of Miami Drosophila labs

Introduction

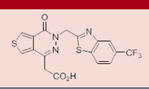
Sorbitol dehydrogenase (SORD) deficiency has been identified as the most frequent autosomal recessive form of hereditary neuropathy, affecting roughly 10,000 patients worldwide. Loss of SORD causes high sorbitol levels in cells due to the inability to convert sorbitol to fructose in the two-step polyol pathway, leading to neurodegeneration. However, underlying mechanisms of sorbitol-induced neurodegeneration have not been fully elucidated.

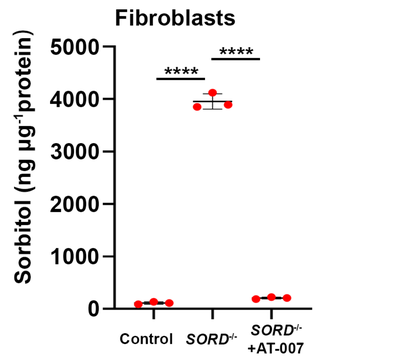


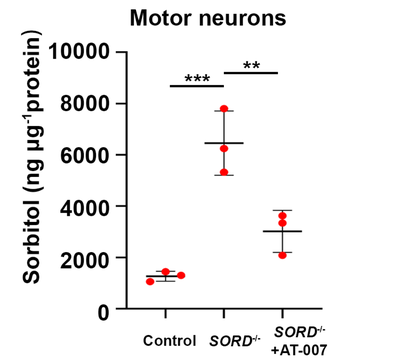
Method

A *Drosophila* model of SORD deficiency was characterized by locomotor assay and brain imaging. Reactive oxygen species (ROS) staining in the brain and muscle 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-derived fibroblasts and flies. Sorbitol levels in cells and fly brains were measured, and neurological phenotypes of flies were analyzed.

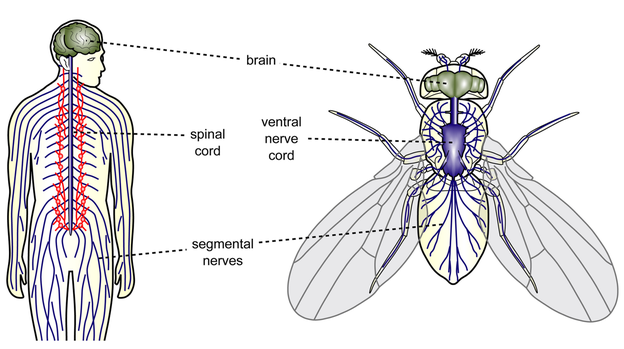
AT-007 reduces sorbitol in patient cells

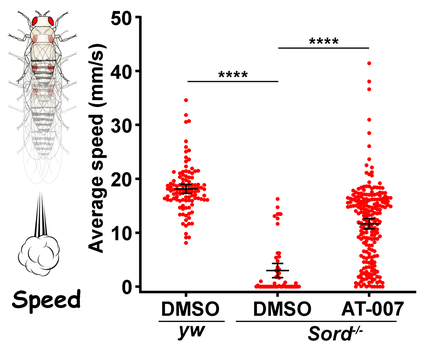
Structure		**Dosing**	Once daily
IC_{50}	0.10 nM	**Formulation**	Liquid Suspension
Half-life	~15 hours	**CNS Penetrant**	Yes

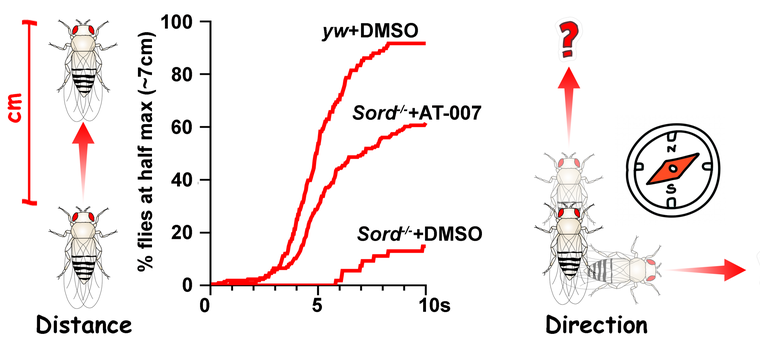


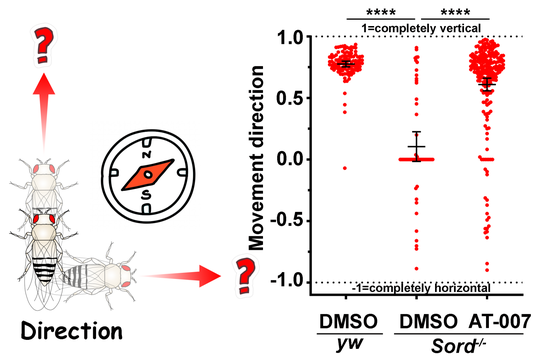


AT-007 improves locomotor activity

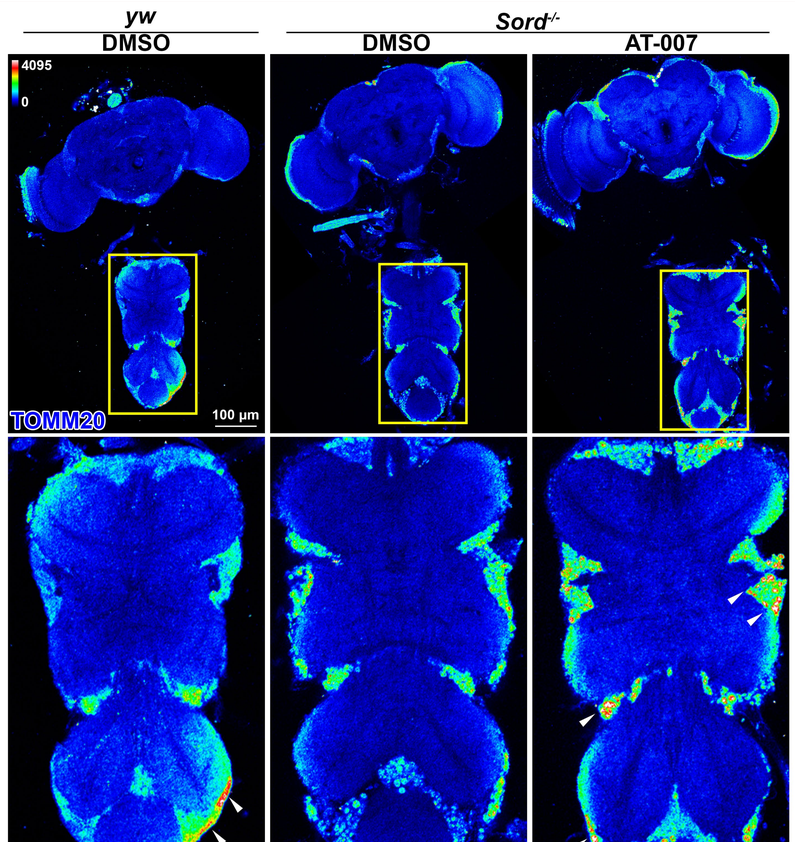


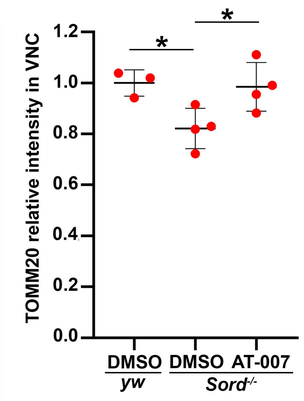


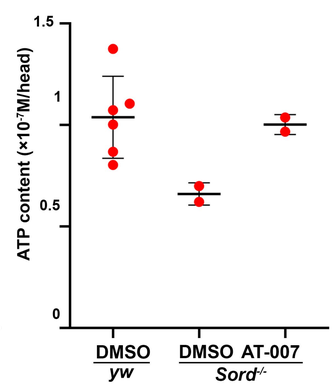


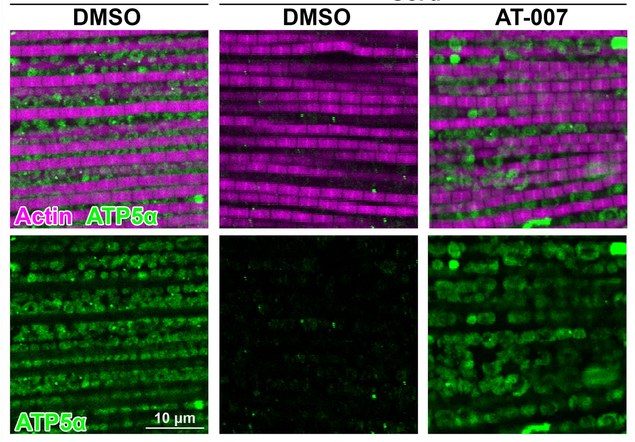


AT-007 rescues mitochondrial dysfunction

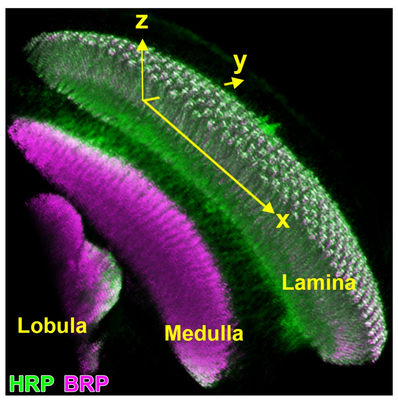


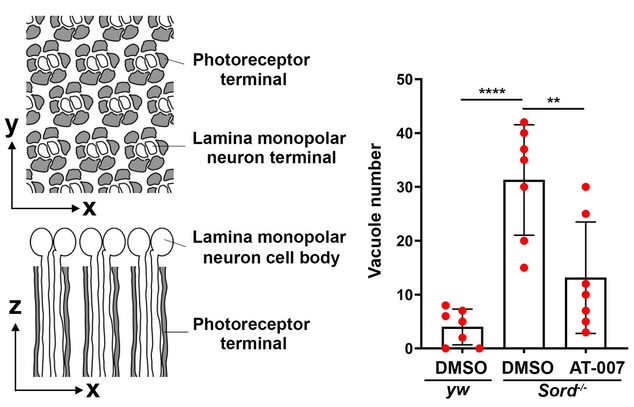


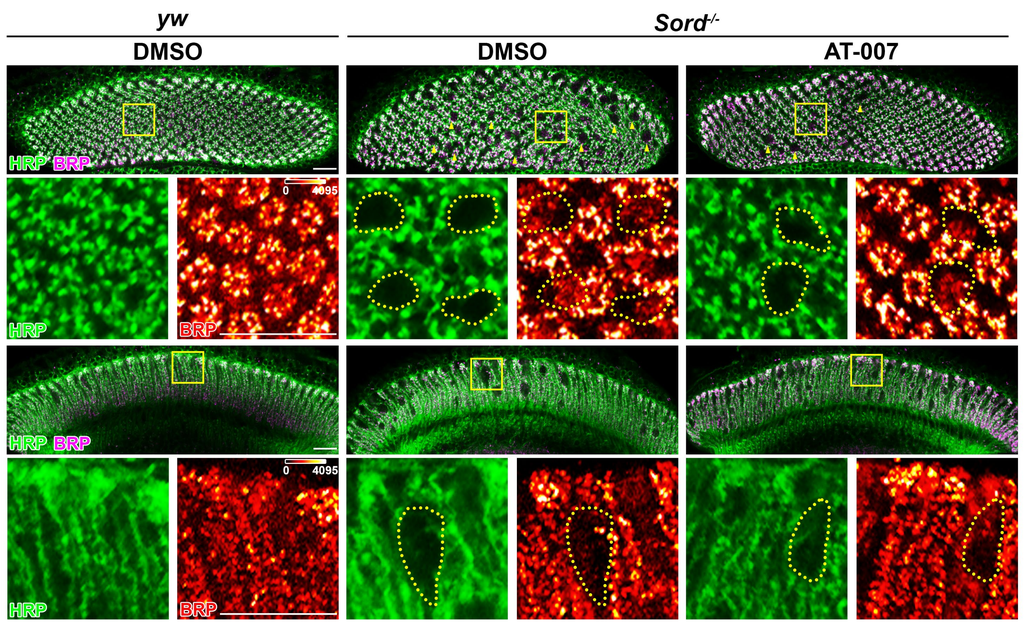




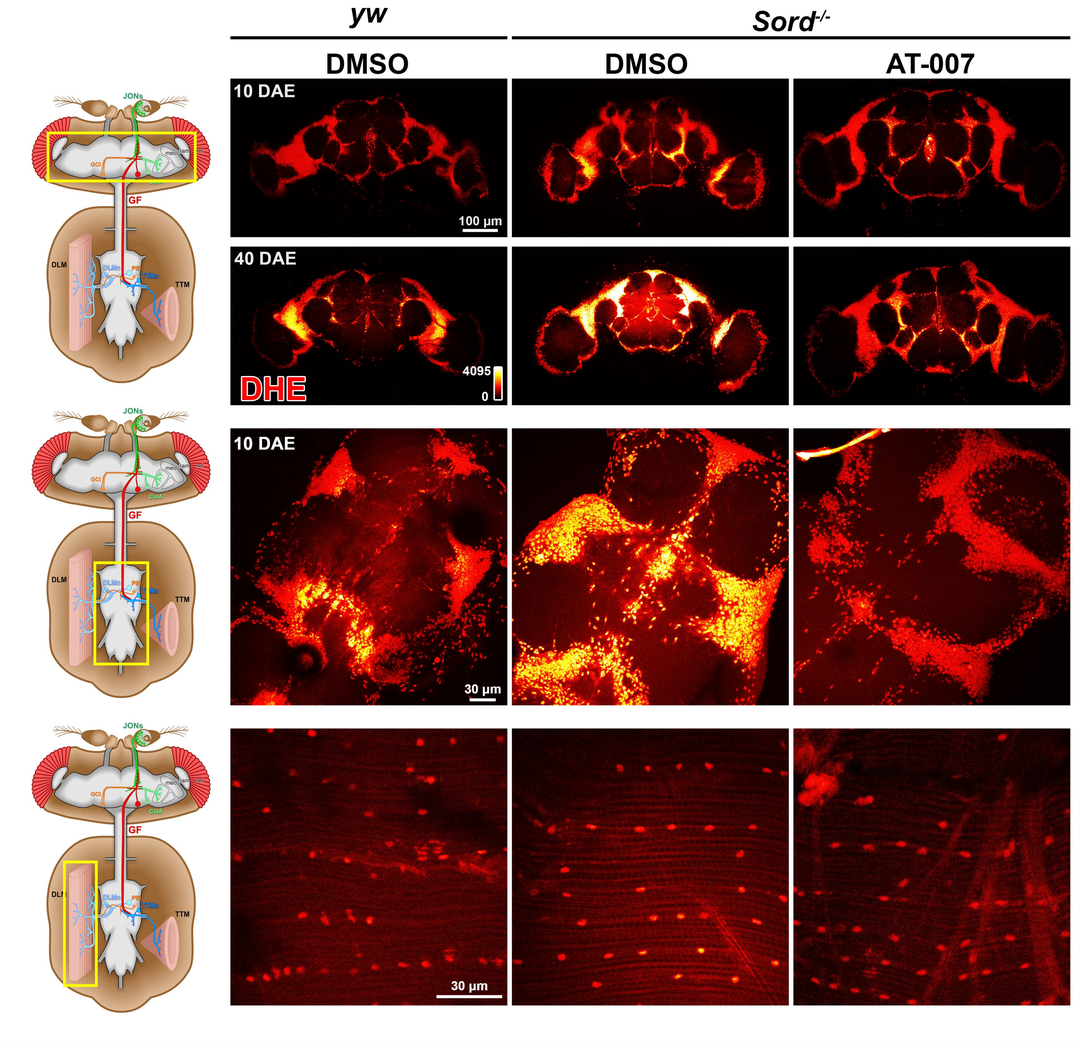
AT-007 alleviates synaptic degeneration

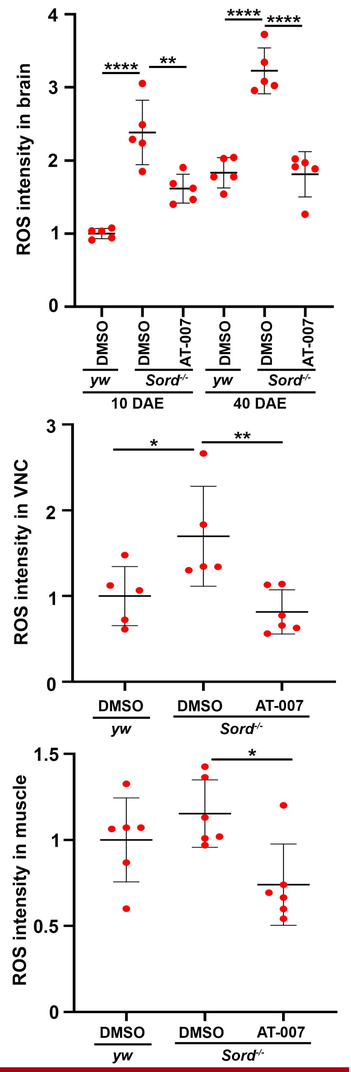






AT-007 reduces ROS accumulation





Summary

- AT-007 significantly reduced sorbitol levels in patient-derived fibroblasts and motor neurons.
- AT-007 feeding significantly improved locomotor activity, mitigated synaptic degeneration, rescued mitochondrial dysfunction, 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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