A Novel Approach to Treatment for ALS through Metabolomics in a Drosophila Model

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that leads to severe metabolic deficits. This project investigates the molecular mechanisms of metabolic dysregulation in ALS to identify potential treatment strategies. Experiments were conducted to determine if previously identified deficiencies in glucose and lipid metabolism can be corrected through diet and genetic intervention using a Drosophila model, which recapitulates key aspects of the disease. High sugar and high fat diets were fed to a group of control flies (w1118) and two models of ALS, each expressing a different allele of TDP-43 (TDP-43WT and TDP-43G298S), a gene linked to the majority of ALS cases. Additionally, the human glucose transporter Glut4 was co-expressed with TDP-43 to determine if glucose import directly into affected cells is protective. Results showed that locomotor deficits are corrected by improving glucose metabolism through diet and genetic intervention. Specifically, a high sugar diet and overexpression of Glut4 are neuroprotective; a significant improvement in locomotor function was observed on a high sugar diet when TDP-43 was expressed in motor neurons. Additionally, different cell types respond differently to diet or genetic intervention; overexpression of Glut4 significantly improved locomotor function in flies expressing the wild type version of TDP-43 (TDP-43WT) in motor neurons, while flies expressing the mutated version of TDP-43 (TDP-43G298S) showed improvement when Glut4 was expressed in glial cells. These results are critical to understand the molecular mechanisms and to develop treatment strategies for ALS and other diseases with TDP-43 pathology including Alzheimer's, and Parkinson's.

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