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Activating Neuroprotective Effects of Glial Cells in Vps13D-associated Ataxia

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Ataxia is a common symptom among many neurological conditions. Due to its high prevalence and quality of life impact, there is significant interest in understanding the underlying cause, as well as potential therapeutic approaches to mitigate its severity. Our lab uses a model of Vps13D-associated ataxia in the fruit fly, Drosophila Melanogaster, which recapitulates aspects of the human disease including age-dependent motor deficits.

The anti-oxidant compounds gastrodin and 4-HBA were found to have neuroprotective effects in *Drosophila* and mouse models of Parkinson's disease. Previous work has demonstrated that these compounds can activate the Nrf2-pathway, a master regulator of anti-oxidant defenses. These compounds are believed to act through supportive glial cells, upregulating their anti-oxidant associated assistance of degenerating neurons.

We supplemented Drosophila diet with low-dose (0.1mM) and high-dose (1mM) concentrations of gastrodin and 4-HBA to determine the impact of these compounds on ataxia in our animal model. Flies' motor ability was tested through negative geotaxis assays at one and two weeks of age. Supplemented animals were compared to untreated controls.

We found that low-dose gastrodin may improve motor function in later life. In addition, low-dose 4-HBA supplementation may improve motor function early in the disease course. Gastrodin is a glycoside precursor of 4-HBA, so these data are interesting in their differing temporal effects. The lack of similarity may indicate a complex metabolic pathway or extensive interactions within glial cells. These data lay the foundation for further investigation into the possibility of glial cell antioxidant activation in the treatment of neurodegenerative ataxia.