

Alpha-Lipoic Acid Treatment of *Drosophila melanogaster* as a Novel Therapeutic Method Targeting mTOR-Associated Cognitive Deficits in Fragile X Syndrome

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Fragile X Syndrome (FXS) is the most common inherited cause of Autism Spectrum Disorder. FXS is caused by transcriptional silencing of the FMR1 gene, which leads to the loss of the translational inhibitor FMRP, which has been implicated in hyperactivity of the mGluR signaling pathway. mGluR-targeted drugs have thus far met with limited success, and alternative pathways must be sought to further FXS treatment. This study proposed that mTOR, a target downstream of mGluR which has demonstrated similar hyperactivity, may serve as a more direct pathway to correct aberrant protein synthesis. Using Alpha-lipoic acid (ALA), which has previously been shown to reduce mTOR signaling, dFMR1 mutant *Drosophila* were evaluated using social space, light-dark, and locomotion assays. Preliminary results showed that all mTORC1-associated phenotypes, including social impairments and circadian rhythm dysregulation, were restored, while the mTORC2-associated phenotype, locomotor dysfunction, was exacerbated. Using a computational model, the study showed that ALA had stronger binding affinity with mTORC1 than it did with mTORC2. Thus, the study initially hypothesized that since the two complexes are differentially regulated, ALA might show direct therapeutic binding between ALA and mTORC1 and thus improving mTORC1-associated phenotypes only. However, the mechanism underlying the therapeutic action still remained unclear. Using mass spectrometry, the study observed the down-regulations of both PIP2 and eIF4G in ALA-treated flies, showing evidence of restored regulations of mTORC1-initiated translations. In conclusion, the study uncovered a potential new clinical path in Fragile X Syndrome, but further investigation is needed to explore modified treatments that could target both complexes.

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