

# The Effect of $\alpha$ -ketoglutarate on a Tau-Based Model of Neurodegeneration in *Drosophila melanogaster*

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The  $\alpha$ -ketoglutarate dehydrogenase complex (KGDHC) enzyme – involved in the Krebs cycle – has been shown to have significantly decreased activity that is thus far unexplained in Alzheimer's disease (AD), a neurodegenerative disease without effective treatment, but supplementation of  $\alpha$ -ketoglutarate ( $\alpha$ KG), its substrate, may promote activity. It was hypothesized that *Drosophila melanogaster* flies expressing human tau protein would experience altered disease progression if fed a diet supplemented with  $\alpha$ KG. To obtain the desired genotype, a cross to express human tau in flies' motor neurons was conducted. For four weeks, the flies' motor function was assessed in larvae and adults and their lifespans recorded. Results show that  $\alpha$ KG supplementation at 5  $\mu$ M and 200  $\mu$ M improved motor function in larvae by 98.14% and 88.05% respectively. In adult flies expressing tau, males on 5  $\mu$ M supplementation experienced motor function 6.83 times better than controls on Week 1, but this improvement lost significance by Week 2. However, while males supplemented with  $\alpha$ KG seem to experience improved pathology initially, females at 5  $\mu$ M experienced lifespans shortened by 8.58 days on average. The data supports the hypothesis that  $\alpha$ KG supplementation does affect AD pathology: in males, benefits are primarily in early stages of disease, and in females, effects are detrimental. These findings highlight the potential of  $\alpha$ KG supplementation as a simple and cost-effective Alzheimer's intervention in early stages. Moreover, this research demonstrates the powerful impact of KGDHC dysregulation on AD pathology, highlighting the need to develop treatment methods targeting its decreased activity.