Alzheimer's and Drosophila: Effect of Age on Efficacy of Treatment in a Model System

Paietta, Elise

Alzheimer's disease is a progressive and primarily age-dependent neurodegenerative disease that is the sixth leading cause of death in the US. An aged-onset model of Alzheimer's disease in Drosophila melanogaster in which the human proteins APP (amyloid precursor protein) and BACE1 (beta-site APP cleaving enzyme) were expressed at a low level in the fly central nervous system was used to test the hypothesis that pharmacological treatment with an inhibitor known to prevent amyloid beta peptide aggregation will slow down the progression of the disease. Further, the hypothesis that beginning such treatment early in the disease process will further delay the onset of behavioral deficits was tested. The affected flies (elav-GAL4; UAS-APP; UAS-BACE) showed the progressive age-dependent development of defects in central nervous system function as tested by (a) a climbing (or locomotive) assay, (b) associative olfactory learning (using electric shock paired with odorants)/short-term memory, and (c) aversive phototaxic suppression. Treatment with D737, an Abeta peptide aggregation inhibitor, suppressed these Alzheimer's-related behavioral phenotypes. The most pronounced behavioral improvement was observed in affected flies continuously treated with D737 starting from Day 0 and Day 10. A reduction in treatment effectiveness was observed with treatment starting points from Day 20 to Day 40, and eventually little difference was observable between treated and untreated affected flies. The results show that an amyloid peptide aggregation inhibitor was most effective in reducing Alzheimer's symptoms at a relatively early stage in the disease progression. At least in aged Drosophila, once major behavior deficits occurred then there was little to no effect of the treatment.