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(in the field of Genetic)

Title:

# Evaluation of relationship between age and splicing of mRNA of *XBP1* gene in the *Drosophila melanogaster* Alzheimer's model

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**Abstract**

**Studying the mechanisms and cellular pathways involved in Alzheimer's disease can be of great help in the treatment of this disease. One of the causes of Alzheimer's disease is a mutation in the Tau protein. In this study, we investigated the mechanism of endoplasmic reticulum stress during tau assembly of human mutant (Tau r406w) with emphasis on *Drosophila* XBP1s gene expression. The XBP1 gene is naturally expressed in the cell but is re-processed during stress (XBP1s). Protein derived from the XBP1s (splice) gene is a transcription factor, and as endoplasmic reticulum stress increases, protein expression also increases. In Alzheimer's disease, the protein is phosphorylated by Tau. Hyperphosphorylated protein aggregates cause endoplasmic reticulum stress. Stress activates the UPR pathway and tries to reduce Tau accumulations by activating XBP1s from the Ire1 branch and if the cell fails to relieve stress, the cell eventually progresses to cell death. In this study, we confirmed the accuracy of the model by expressing the mutated version of the human Tau r406w gene in Drosophila eyes. Tau expressing flies in central nervous system neurons were divided into in 3 age groups of 10, 20 and 30 days were examined by behavioral tests and molecular analyzes. Real time PCR technique and enzymatic digestion were also performed for the PCR product for the XBP1 gene to isolate the desired XBP1s fragment from XBP1u. Gene expression studies revealed that expression of XBP1s and XBP1u genes was significantly increased with increasing age and expression of Tau r406w protein in Drosophila neurons. The results indicated the role of endoplasmic reticulum stress in Tau gene pathogenesis which was positively correlated with aging. Thus, Taupathy damages the nervous system under the increasing effects of aging and stress activation of the endoplasmic reticulum.**

**Keywords: Alzheimer's disease, XBP1s, *Drosophila melanogaster*, Aging**