ABSTRACT:

Dementia is a type of neurological disorder which characterized by progressive and irreversible impairment in consciousness, memory, social skills, and control of emotional reactions. Aetiology of dementia is highly heterogenous and it mainly occurs secondary as the result of genetic and non-genetic factors.Alzheimer's disease(AD) is the most common cause of dementia.The hallmarks of AD include extracellular amyloid beta plaques and neurofibrillary taue tangles.To date, it has been identified that polymorphism of Apolipoprotein E(APOE) is the most important genetic risk factor of AD. Between three isoforms of APOE (E2,E3 and E4)the frequency of E4 allele in sporadic or late onset Alzheimer's patient is more than healthy people.Definite relation between APOE4 and AD remains obsecure.Another major cause of AD which had been noticed in recent years, is Endoplasmic reticulum stress(ER stress).Acceleration of production of protein versus it's folding and maturity leads to ER response.This response may play a role in AD.In this research, possible interaction of E3 and E4 alleles of APOE gene with ER stress has been studied. The alteretion level of ATF4, ATF6 and XBP1expression in transgenic Drosophila-melanogaster have been studied.Behavioral testing of larvae revealed that neuronal APOE4 expression decreased learning and memory. The memory of larvae expressing APOE3 in their neuroglial cells showed improved memory by applying heat shock. Ethanol sensitivity test revealed that expression of APOE4 increased the time of recovery in both males and females. Whereas recovery time in males was longer than females due to genetic differences. By lipid profile test it was found that expression of APOE4, increases triglyceride (TG) and cholesterol (Chol) levels in neurons But APOE3 expression increases both TG and Chol levels in neurons and glia. Expression of APOE3 and APOE4 had no effect on HDL level.The levels of three biometals; Zinc, Iron and Copper were measured in Drosophila brain and it was found that expression of APOE4 would not change the homeostasis of these three metals. Molecular analysis of APOE3 expression showed increased ATF4 gene expression in neurons and glia. However,APOE4 expression decresed ATF4 expression. APOE4 expression had no effect on AFT-6 gene expression but APOE3 increased its expression in glial cells. XBP1 expression level has been increased by APoE3 over-expression and has been decreased following APOE4 over-expression. Thus, it can be concluded that APOE4, would change the phenotypic, biochemical and molecular changes by disruption in lipid composition in the Drosophila model. In glia, APOE3 expression induces ER stress but the results can not be concluded on the effect of APOE4 on ER stress induction.

Keywords: Alzheimer'disease, *APOE* gene, *Drosophila melanogater*, Endoplasmic reticulum stress

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