High Saturated Fat-Enriched Diet Evokes Endoplasmic Reticulum Stress and Consequently Increases β- Site App Cleaving Enzyme 1 Activity in Amyloid-Beta Engenderment in the Brain

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Alzheimer's disease (AD) is the most common form of dementia in the elderly that is histo-pathologically characterized by extracellular accumulation of aggregated Amyloid-β (Aβ) peptide as neuritic senile plaques and the intracellular accumulation of aggregated hyperphosphorylated protein tau (τ) as neurofibrillary tangles. The aspartyl protease BACE1 is indispensable for the engenderment of Aβ and catalyzes the rate-limiting step in Aβ genesis from AβPP. The expression of BACE1 protein as well as its enzymatic activity is significantly augmented in the AD brain. The etiology of AD is multifactorial and egregiously comprehended, but epidemiological studies have implicated a diet rich in saturated free fatty acids (sFFA) as a significant risk factor for developing AD. Palmitic acid (palmitate) is the most abundant long-chain free saturated fatty acid in the brain and the diet and higher palmitate levels in the plasma, as observed in obesity and diabetes, inversely correlate with cognitive function. Recent cogent evidence has implicated endoplasmic reticulum (ER) stress as one of the culpable factors in initiating and fostering the deleterious neurodegenerative changes in AD. A multitude of studies have cogently demonstrated that sFFA such as palmitic acid evoke ER stress. In this study we demonstrate that palmitate evokes ER stress leading to the induction of CHOP expression which indispensably mediates the up-regulation in BACE1 expression and Aβ engenderment via the NF-κB signaling pathway. Our study unveils a novel ER stress/CHOP/NF-κB signaling pathway and delineates the molecular mechanism thereof that mediate the palmitate-induced up-regulation of BACE1 expression.