The saturated free fatty acid palmitate increases Amyloid-β genesis through SREBP1 expression and activation

O. Ghribi
Department of Biomedical Sciences, University of North Dakota School of Medicine, USA

The etiology of Alzheimer's disease (AD) is multifactorial and likely involves a dynamic interplay between a myriad of risk variables that include genetic, environmental, and life style including dietary factors. Epidemiological studies have implicated saturated fat-enriched diets in the etio-pathogenesis of AD. Diets rich in saturated fatty acids, such as palmitate, have been shown to cause cognitive dysfunction characterized by learning and memory deficits in several rodent models. However, the molecular mechanisms that underlie the deleterious role of palmitate-enriched diets in the augmentation of BACE1 expression and Aβ genesis is egregiously comprehended. In this study, we determined the role of SREBP activation in the palmitate-induced increase in BACE1 expression, activity, and subsequent Aβ genesis. We fed nine-month old C57BL/6J mice a palmitate-enriched diet or the respective control-chow diet for three months and determined the extent to which increased SREBP1 and SREBP2 expression as well as transcriptional activity plays a role in the palmitate-enriched diet-induced increase in BACE1 expression, BACE1 activity, and Aβ genesis in the hippocampus. We also determined the role SREBP1 and SREBP2 activation in the induction of BACE1 expression, BACE1 activity, and Aβ genesis in exogenous palmitate-treated mouse Neuro-2a (N2a) neuroblastoma cells and delineated the underlying mechanisms involved. Our data shows that palmitate-induced SREBP1 activation, but not palmitate-induced SREBP2 activation, directly regulates BACE1 expression at the transcriptional level. Knocking-down SREBP1 or ectopic expression of the dominant negative SREBP1 mutant, but not SREBP2, significantly mitigated the palmitate-induced increase in BACE1 expression, BACE1 activity, and subsequent Aβ genesis. Our study elucidates a novel signaling target, the transcription factor, SREBP1, as a unique downstream effector of palmitate-induced up-regulation in BACE1 expression and subsequent Aβ genesis.