EXPRESSION OF GENES RELATED TO BETA AMYLOID PEPTIDE METABOLISM AND APOPTOTIC PROCESS IN A MOUSE MODEL OF FAMILIAL HYPERCHOLESTEROLEMIA

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Familial hypercholesterolemia (FH) is caused by inherited genetic abnormalities that directly and indirectly affect the function of low density lipoprotein receptor (LDLr). Recent evidence reported that middle age patients with FH show a high incidence of mild cognitive impairments, a prodromal stage of abnormal cognitive performance, which precedes Alzheimer’s disease. We corroborated this observation in an experimental model of FH, the LDLr knockout mice (LDLr\(^{-/-}\)). In addition, we observed that the LDLr\(^{-/-}\) mice are more susceptible to beta amyloid peptide (A\(\beta\)) neurotoxic effects. Herein, we evaluated the hypothesis that the cognitive impairments of young (3-month-old) and middle-aged (14-month-old) LDLr\(^{-/-}\) mice are related to altered brain gene expression of proteins involved in A\(\beta\) metabolism and apoptotic process. The animal’s prefrontal cortex and hippocampus were dissected to determine the mRNA levels of amyloid protein precursor (APP), \(\beta\)-secretase (BACE-1), preselinin-1 (PS-1) and apoptosis-related proteins (Bax-1 and Bcl-2) by qPCR. The LDLr\(^{-/-}\) mice, independent of the age, did not present alterations in the APP mRNA levels in the prefrontal and hippocampus. In relation to BACE-1 gene expression, the absence of the LDLr induced a significant increase in mRNA levels of BACE-1 in the prefrontal cortex of young animals. Notably, the PS-1 gene expression was significantly increased in the brain structures of the middle-aged LDLr\(^{-/-}\) mice. Finally, the hypercholesterolemic mice, already in three-month-old, presented a decreased mRNA Bcl-2/Bax rate levels in the prefrontal cortex and hippocampus. The cognitive impairments in the LDLr\(^{-/-}\) mice appears to be associated with increased A\(\beta\) processing and apoptosis induction in brain regions related to memory formation.

Key Words: Familial hypercholesterolemia, Alzheimer’s disease, Beta amyloid peptide.