Familial hypercholesterolemia (FH) is a lipoprotein metabolism’s disorder caused by genetic abnormalities that affect the function of the low density lipoprotein receptor (LDLr). This condition is characterized by high plasma cholesterol concentrations and premature atherosclerosis development. Recently, clinical and preclinical studies have demonstrated an association between FH and mild cognitive impairment, considered a transitional stage between normal aging and early-stage Alzheimer’s disease. Previously, we observed that in a mouse model of FH, LDLr knockout mice (LDLr\(^{-/-}\)), the cognitive deficits were related to an increased hippocampal blood brain barrier (BBB) permeability. Herein we aimed at investigating the cognitive function and BBB integrity more accurately in the LDLr\(^{-/-}\) mice. To this end, we exacerbated the hypercholesterolemia in the LDLr\(^{-/-}\) mice using a thirty-day-treatment with a hypercholesterolemic diet. After the treatment, the C57BL/6 wild type and LDLr\(^{-/-}\) mice were submitted to the spatial and working memory paradigms. In addition, the BBB permeability to sodium fluorescein and tight junction proteins gene expression were evaluated in the prefrontal cortex and hippocampus of mice. Of note, the LDLr\(^{-/-}\) mice treated with the hypercholesterolemic diet presented tenfold elevation in the plasma cholesterol levels, while in the wild type mice the hypercholesterolemic diet exposure caused only a moderate increased in the plasma cholesterol levels and did not induce cognitive impairments. The LDLr\(^{-/-}\) mice regardless of the diet presented spatial and working memory impairments. We observed an increased BBB permeability to sodium fluorescein in prefrontal cortex and hippocampus and a decrease in the hippocampal claudin-5 and occludin mRNA levels in both wild type and LDLr\(^{-/-}\) mice treated with hypercholesterolemic diet. Actually, the BBB disruption was more pronounced in LDLr\(^{-/-}\) mice. Therefore, the BBB damage seems to be an earlier event to the cognitive impairment induced by hypercholesterolemia.

**Key Words:** Familial hypercholesterolemia, Blood brain barrier, Cognitive impairments.