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Evaluation of the Development of Neurodenegenerative Processes in a High-Fat Diet

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Abstract This study evaluated changes in the amount of β-amyloid (Aβ) protein and LRP1 protein, which is involved in its clearance, in a modeled nonalcoholic fatty liver disease (NAFLD) based on a high-fat diet. The results showed that Aβ protein levels gradually increase in blood and brain regions in NAFLD, while LRP1 protein levels decrease in liver, blood, and brain tissues. These changes are associated with impaired Aβ clearance and increased risk of neurodegeneration, confirming the complex interplay between liver dysfunction and brain pathology. The results of the study suggest that β-amyloid and LRP1 proteins may be important biomarkers in the development of neurodegenerative processes in NAFLD. This necessitates the development of therapeutic approaches that target the liver to prevent cognitive impairment associated with NAFLD.

Keywords β-amyloid (Aβ), LRP1 protein, Nonalcoholic fatty liver disease (NAFLD), High-fat diet, Neurodegeneration, Protein clearance

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease. NAFLD affects approximately 25% of the world's population, and this figure is expected to increase to 33.5% by 2030 [1].

Nonalcoholic fatty liver disease is increasingly important in the pathogenesis of neurodegeneration and is a risk factor for mild cognitive impairment and dementia.

Dementia is a common disease worldwide, with an estimated 50 million people suffering from dementia and this number is expected to increase annually [2]. According to the World Health Organization, the number of people with dementia will reach 82 and 152 million by 2030 and 2050, respectively [3].

NAFLD is associated with a decrease in the hepatic expression of proteins involved in the clearance of circulating β-amyloid (Aβ) (LRP1-low-density lipoprotein receptor-related protein, LDLR-low-density lipoprotein receptor) and Aβ catabolism (insulin-degrading enzyme-IDE, neprilysin-NEP). Impaired hepatic Aβ degradation may contribute to the increase in circulating Aβ, which may contribute to the increased accumulation of Aβ in the brain and the development of Alzheimer's disease [4,5]. The involvement of Aβ, LRP1 and ApoE (especially the ApoE4 allele) in the pathogenesis of neurodegeneration and Alzheimer's dementia is very complex and requires further studies.

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2. Purpose of the Research

The purpose of this study was to investigate the relationship between nonalcoholic fatty liver disease (NAFLD)—induced by a high-fat diet—and the accumulation of β-amyloid (Aβ) protein alongside the reduction of LRP1 protein, a key mediator in Aβ clearance. Specifically, the research aimed to evaluate changes in Aβ and LRP1 levels in the blood, liver, and brain tissues in a NAFLD model.

3. Materials and Methods

8-10-week-old male Wistar rats were used as subjects. The experimental fatty liver hepatosis model was induced by daily supplementation of melted beef fat to the animal diet based on a high-fat combined diet and by giving 10% fructose and 10% glucose solution instead of water.

On the appropriate days of the study, the rats were decapitated in a cold room at a temperature of 0°-+2℃ and the blood of the animals was collected. Then, the collected blood was left at +4℃ for 30 minutes, centrifuged at 3000 rpm, and the serum was collected. The brain and liver were isolated in the cold, washed in Tris-HCl buffer, pH 7.4, and frozen in liquid nitrogen. The amount of β-amyloid in the serum, cerebral cortex, and hippocampus, and the amount of LRP1 in the serum, liver, cerebral cortex, and hippocampus were determined.

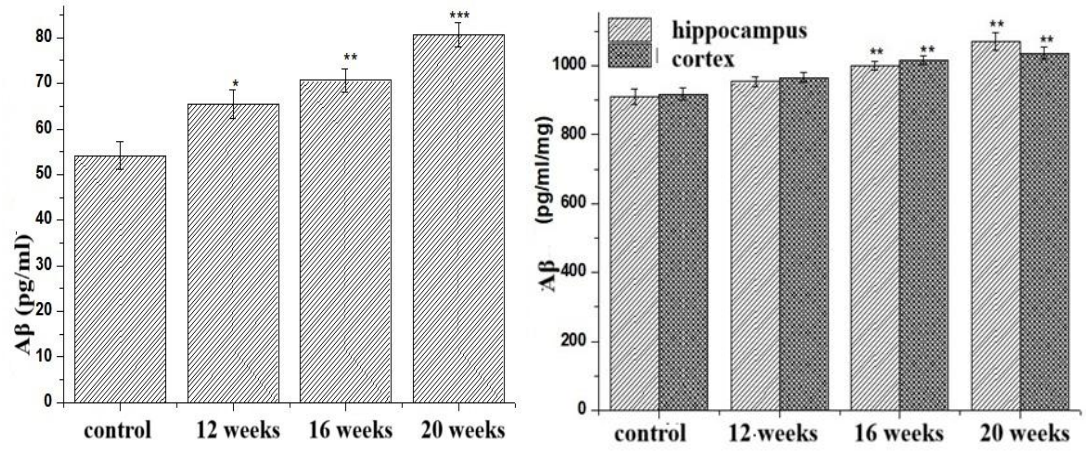

Figure 1. Dynamics of Aβ in experimental NAFLD

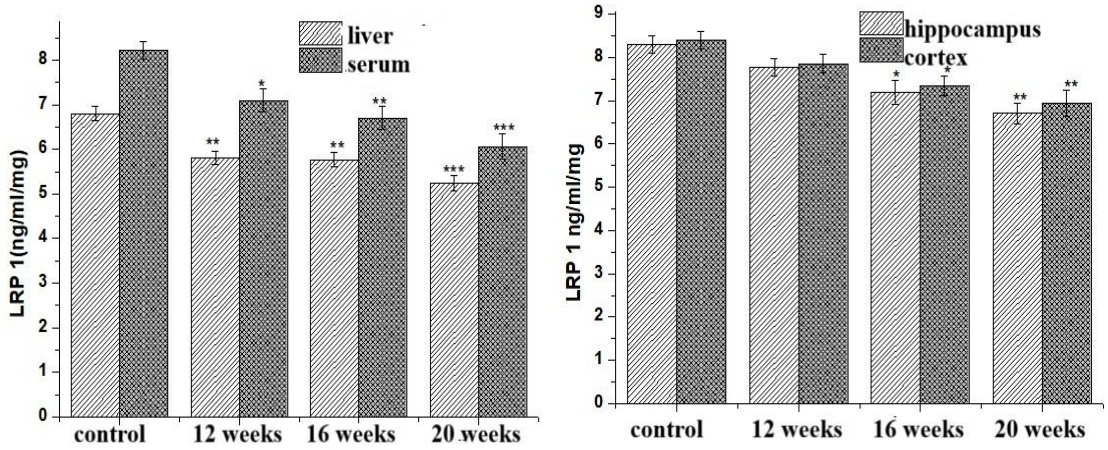

Figure 2. Dynamics of LRP 1 protein in experimental NAFLD

4. Results and Discussion

Neurodegenerative processes are characterized by the accumulation of amyloid as a result of impaired clearance of pathological β-amyloid protein. Therefore, β-amyloid protein is a very important indicator in the diagnosis of neurodegenerative diseases. For this reason, we also determined the amount of β-amyloid protein, which indicates the development of neurodegenerative processes. The results of our studies showed an increase in the levels of this protein in the serum, hippocampus and cortex of the brain in fatty hepatosis (Figure 1). In particular, at 12, 16 and 20 weeks of our study, the levels of β-amyloid protein in the serum increased by 20.7%; 30.33% and 48.81% compared to the intact group; in the hippocampus it increased by 4.81%; 9.86% and 17.6%. In the area of the cerebral cortex, β-amyloid protein values are 5.14%, respectively; It was found to increase by 10.59% and 12.8%.

Also, a decrease in the amount of the LRP1 receptor, which carries out the clearance of amyloid protein in the liver, was found in NAFLD. In particular, in the group fed with YFP, the amount of LRP1 in liver homogenate decreased by 13.62%; 18.49% and 26.28% compared to the intact group at 12, 16 and 20 weeks, while in blood serum it decreased by 14.55%; 15.15% and 22.94% (Figure 2).

The amount of LRP1 protein in the hippocampus of the brain decreased by 6.38%; 13.37% and 19.16%. In the cortex, it decreased by 6.43%; 12.5% and 17.38%.

The results of our study show that in NAFLD, an increase in the amount of β-amyloid protein was detected in the hippocampus and cortex of the brain, and, conversely, a decrease in the amount of LRP1 protein, which is involved in the clearance of β-amyloid protein, was detected in the brain and liver tissue.

Dyslipidemia and disorders of cholesterol metabolism are very important in the development of neurodegeneration in NAFLD patients. LRP1 is involved in the clearance of β-amyloid (Aβ) from the central nervous system. One of the main functions of the liver is detoxification, which is important in the clearance of circulating soluble Aβ. In liver diseases, there is a decrease in the ability of detoxification, and as a result, there is an increase in the concentration of Aβ in the blood. The absorption of Aβ protein from the blood is carried out through LRP1 and low-density lipoprotein receptors, which are abundant in hepatocytes. Liver dysfunction and hepatic insulin resistance have been shown to inhibit the clearance of Aβ from the blood by reducing the amount of LRP1 in the liver and the translocation of LRP1 to the

hepatocyte membrane [6].

Under normal conditions, β-amyloid is produced and eliminated by the body in a balanced manner. However, conditions such as metabolic syndrome, insulin resistance, and lipid metabolism disorders can upset this balance and cause the accumulation of Aβ peptide [7]. Studies have shown that β-amyloid peptide degradation is impaired and its amount is increased in the brain in patients with YG and in animal models [8].

In our study, increased glucose levels were observed, which indicates the development of insulin resistance. Previous studies have confirmed the direct relationship between insulin resistance and β-amyloid accumulation. When insulin receptor activity decreases, the activity of the insulin-degrading enzyme (IDE), which regulates the degradation of β-amyloid, decreases, resulting in reduced Aβ degradation and increased Aβ accumulation [9]. Insulin deficiency and impaired glucose utilization cause memory impairment similar to that observed in Alzheimer's disease. Insulin regulates tau protein phosphorylation and β-amyloid clustering in the brain, and therefore insulin resistance directly affects Aβ accumulation in the brain. Several studies have shown that cholesterol and triglyceride levels increase in animals fed a high-fat diet. This may be due to the reduced degradation of Aβ by low-density lipoprotein. Increased cholesterol can promote Aβ synthesis and reduce its clearance from the brain [9]. Increased levels of cholesterol in the blood and brain support its role in Aβ accumulation.

LRP1 is a multifunctional endocytosis receptor that is involved in the metabolism of lipoproteins, amyloid (Aβ), metalloproteinases, and several other important molecules. It is abundantly expressed in neurons and astrocytes in the brain and in hepatocytes in the liver. Several studies have shown that LRP1 plays an important role in Aβ clearance, and its reduction may therefore enhance the pathophysiological mechanisms leading to Alzheimer's disease [10]. Several studies have shown that LRP1 deficiency is associated with hepatic steatosis and metabolic syndrome [11].

LRP1 plays an important role in Aβ clearance in the brain and also affects neuronal plasticity and synaptic function. Birnbaum et al. (2018) reported that LRP1 is downregulated in the hippocampus and cortex in Alzheimer's disease [12,13-16].

Thus, in AD, a decrease in the hepatic levels of proteins involved in the clearance of circulating Aβ proteins (LRP1, LDLR) leads to neurodegeneration. These findings support the validity of our study. It should be noted that, given the localization of the LRP1 receptor, which clears Aβ from the blood, liver-targeted therapy is appropriate for the treatment of neurodegenerative disorders [17,18].

5. Conclusions

In fatty liver disease, an increase in the amount of β-amyloid protein in the serum and brain, and a decrease in the amount of LRP1 protein, which clears them, were found in the liver and blood. The obtained results indicate the development of neurodegenerative processes in a high-fat diet.

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