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NEURODEGENERATION AS A COMPLICATION OF NONALCOHOLIC FATTY LIVER DISEASE (Review article)

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is now characterized as the hepatic manifestation of metabolic syndrome, is the leading cause of liver cirrhosis and currently affects a quarter of the world's population. A number of recent studies have focused on the prevalence of neurodegeneration, including dementia and cognitive impairment in NAFLD. Various risk factors, including insulin resistance, cerebrovascular dysfunction, intestinal dysbiosis, hyperammonemia, neuroinflammation and etc. Given the prevalence of NAFLD, its negative impact on cognitive function is a medical problem with enormous social and economic consequences. This article reviews the available evidence for the role of NAFLD in the development of neurodegeneration and describes possible mechanisms involved in the development of brain dysfunction in NAFLD.

Key words: nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, dementia, cognitive disorders, insulin resistance, neuroinflammation, neurodegeneration, liver-brain axis.

INTRODUCTION

Currently, NAFLD is the most common chronic liver disease. Approximately 25% of the world's population is affected by NAFLD, is expected to increase to 33.5% by 2030 [66]. 70% of all liver diseases correspond to fatty hepatosis [67]. The sharp increase in the prevalence of NAFLD is closely related to the increase in obesity in the world, the pathogenesis of the disease is closely related to the metabolic syndrome and insulin resistance. One of the main causes of liver cirrhosis is NAFLD. Because, NAFLD is characterized by the accumulation of triglycerides in the liver and can progress from simple fatty steatosis, steatohepatitis to fibrosis and eventually cirrhosis which can progress to

hepatocellular carcinoma. Although hepatic steatosis is usually reversible, approximately, one-third of patients with NAFLD progress to nonalcoholic steatohepatitis (NASH) leading to severe cirrhosis or hepatocellular carcinoma. The mechanisms of the transition of NAFLD to NASH are not fully known, but the role of lipotoxicity, oxidative stress and anti-inflammatory mediators in the development of this disease has been studied [19]. People's lifestyle, eating habits and genetic background play an important role in the incidence of NAFLD. Other metabolic diseases such as type 2 diabetes, chronic kidney disease, cardiovascular diseases, and intestinal dysbiosis serve as common risk factors for the occurrence of NAFLD. In addition, NAFLD is also a risk factor for other metabolic diseases. According to researches, more than 50% of patients with diabetes, more than 80% of people with obesity suffer from this disease, and the occurrence of NAFLD in pathological obesity is 95-100%. Often, this disease occurs relatively often in the 40-60 age group of the population [55]. It should be noted that NAFLD is no longer considered only a liver disease, as many organ systems play an important role in the pathogenesis of liver inflammation.

Recently, NAFLD has been studied as an important disease associated with the development of neurodegenerative processes, including cognitive impairment and dementia. Also, according to sources, data indicate that dyslipidemic conditions contribute to or serve as a cofactor in the development of Alzheimer's disease [59]. Neurological disorders such as cognitive impairment and memory loss may be associated with insulin resistance, hyperammonemia, vascular dysfunction, gut microbiota disruption, inflammation, and other features observed in patients with NAFLD [55]. Phenotopic manifestation of NAFLD is associated with obesity. Obesity has been shown to increase the risk of developing cognitive decline and Alzheimer's disease six times in adulthood and middle age. Also, obesity in middle age significantly increases the risk of dementia and Alzheimer's disease, unlike obesity in later life [2; 38; 57].

Pathogenesis of NAFLD. Triglycerides (TG) are the main lipid components of the liver, and their accumulation in the liver is observed due to the entry of free fatty acids (FFA) into the liver or an increase in the synthesis of fatty acids from acetyl coenzyme A in the liver itself. The pathogenesis of NAFLD is multifactorial, but insulin resistance and obesity are the main factors in the development of this disease. The safest way to store FFAs is to store them in the form of TG in hepatocellular lipid droplets. Hepatocellular TG comes from several sources: dietary fatty acids; such as increased peripheral lipolysis due to adipose tissue resistance and increased lipogenesis in the liver due to hyperinsulinemia. For this reason, the formation of TG in the hepatocyte is directly related to the amount

of glucose, FFA and acetyl coenzyme A in it. Briefly, the accumulation of fat in the liver can occur through several mechanisms, such as increased lipolysis or increased FFA due to dietary fat consumption, decreased FFA oxidation, increased de novo synthesis of hepatic lipids. increase and decrease in the secretion of very low density lipoproteins (VLDLP) in the liver. If the synthesis of lipids exceeds the synthesis of lipoproteins that excrete them, fat accumulation occurs in the liver. As a result, steatosis develops, which leads to the activation of free radical oxidation of lipids, increased lipid peroxidation (LPO) and the development of apoptotic and necrotic processes in hepatocytes. If inflammation and liver damage are not observed, it does not progress to the next stage of steatosis, activation of inflammatory cytokines and oxidative stress under the influence of free fatty acids. originates. Hepatic accumulation of EIK and cholesterol leads to mitochondrial dysfunction and ER stress, resulting in tumor necrosis factor-α (TNF-α)-mediated liver injury and accumulation of reactive oxygen species (ROS). The gut-liver axis is also affected by food, resulting in microbiota dysbiosis and production of inflammatory cytokines. Multiple receptors (MRs) in the intestinal epithelium can respond to dietary lipids, influencing systemic inflammation and insulin resistance. Adipose tissue is able to produce several mediators, such as leptin, interleukin 6 (IL-6) and TNF-α, which are responsible for the interaction between liver and adipose tissue in the pathogenesis of NAFLD. 15-20% of NAFLD patients develop NASH due to the development of inflammatory processes, if it is not treated in time, it progresses to the stages of NASF (non-alcoholic steatofibrosis) and cirrhosis. In this process, increased oxidative stress (induction of microsomal cytochrome P450) and lipid peroxidation, mitochondrial dysfunction, cytokine/adipokine imbalance, TNF-α, IL-6, adiponectin, lipotoxicity of FFAs, cholesterol accumulation in the liver occur [61] .

So, if overeating and lack of movement are the main factors in the origin of NAFLD, consumption of certain drugs and intestinal dysbiosis take place to a lesser extent. Factors involved in the development of NAFLD include diet, lifestyle, gut microbiota changes, epigenetic and genetic changes, mitochondrial dysfunction, oxidative or endoplasmic reticulum (ER) stress, lipid metabolism disorders, and modulation of the immune system. how many factors are included.

NAFLD as an important disease associated with the development of neurodegeneration. Nonalcoholic fatty liver disease is becoming increasingly important in the pathogenesis of neurodegeneration and is one of the risk factors for the development of mild cognitive impairment and dementia.

Dementia is a prevalent disease worldwide, with approximately 50 million people affected by dementia and this number expected to increase annually [39].

According to the World Health Organization, the number of people with dementia will reach 82 and 152 million in 2030 and 2050 [21]. In addition, as the world's population lives longer, Alzheimer's disease and dementia are predicted to be a major global health problem in an aging world population. It is characterized by mental and cognitive degeneration, which leads to memory loss and cognitive impairment. There are the following types of dementia: Alzheimer's dementia (AD), diabetes-related dementia, and vascular dementia. There is evidence that all types of dementia are related to the pathogenesis of NAFLD.

The hypothesis of a link between AD and NAFLD is very recent, and most studies are conducted in animal models rather than in humans. One of the factors influencing the development of AD in NAFLD is the consumption of a high-fat diet (HFD). NAFLD is mainly modeled in animals using HFD. Many studies have shown that there is a positive correlation between NAFLD and AD [18;32], and high-fat and high-fructose diets have been shown to accelerate cognitive impairment in AD [24;51]. One of the first studies in mice chronically fed FFA showed a time-dependent decrease in brain weight compared to controls. Subtle histopathological abnormalities such as neuronal loss and apoptosis were also found in the brain tissue. Acceleration of neurodegeneration and the formation of β-amyloid protein aggregates has been found after HFD-induced inflammation and the development of NAFLD [35]. In the studies, 4, 8, or 12 weeks of HFD feeding had no effect on brain histopathology. However, 16 weeks of HFD feeding caused neuronal loss, apoptosis, and other subtle histopathological abnormalities [48]. After 20 weeks of HFD feeding, apoptosis was more pronounced in the hippocampus and temporal neocortex, as evidenced by cell loss and increased lipid peroxidation and astrogliosis (GFAP immunoreactivity) in these regions.

In patients with NASH, histological analysis of the cerebellum area revealed the presence of parenchymal microthrombi, neurodegeneration in the Purkinje layer, and glial changes in the molecular layer, in addition to the activation of white matter microglia and astrocytes [5].

Yet other studies have shown no cognitive impairment in patients with simple steatosis. This suggests that simple steatosis may not be an independent risk factor for cognitive dysfunction, and that factors associated with more severe levels of the disease, such as elevated ammonia levels and systemic inflammation, may be required [37].

One of the first affected brain areas in the early stages of chronic liver disease may be the cerebellum, hippocampus, prefrontal cortex (PFC), and other brain regions important for cognition, memory, learning, and mood regulation [42]. In their research, scientists tried to determine which areas of the brain might be

affected by NAFLD, and the result was a decrease in dopamine in certain areas of the brain, such as the prefrontal cortex, hippocampus, and amygdala, and a decrease in noradrenaline in the prefrontal cortex, cerebellum, and striatum. due to decreased metabolic activity [27], neuronal loss in the frontal cortex, astrogliosis [65], dopaminergic neuronal damage [63], another study revealed a decrease in the volume of white and gray matter of the brain [20]. These studies confirm the hypothesis of NAFLD effect in cognitive impairment.

It is worth noting that NAFLD and dementia share many risk factors. The pathogenetic mechanism of dementia is complex, and dementia can appear as a complication of several diseases. Metabolic disorders such as NAFLD have been shown to be significantly associated with an increased risk of dementia [14], whereas some studies have shown no association between NAFLD and cognitive impairment or between NAFLD and dementia [54]. showed that Physically frail patients with a high risk of liver fibrosis have a 5-fold higher risk of receiving a diagnosis of dementia within 8 years, and physical frailty or a high risk of liver fibrosis are independent risk factors [56].

Studies have also reported liver steatosis with increased activity of alanine aminotransferase (ALT), γ-glutamyl transferase (GGT) enzymes in plasma in 76% of patients with amyotrophic lateral sclerosis and patients with motor neuron dysfunction, and they mainly studied patients with behavioral disorders and dementia [10]. Thus, many studies have shown a relationship between NAFLD and cognitive impairment. Currently, there is great interest in studying the relationship between NAFLD and neurodegenerative diseases, probably because these diseases are common worldwide and there is no effective pharmacological treatment for either of them.

Molecular and pathophysiological basis of development of neurodegeneration in NAFLD. The pathogenesis of NAFLD is a very complex process, and the progressive deposition of lipids in the liver leads to the development of lipid peroxidation, insulin resistance, oxidative stress and inflammation. This contributes to peripheral insulin resistance and a low-grade systemic inflammatory state. NAFLD not only affects liver function, but also causes many extrahepatic manifestations, including central nervous system changes, such as depression, cognitive impairment, Alzheimer's disease, and dementia. Also, an important common feature of Alzheimer's disease and NAFLD is a change in lipid metabolism, which alters the function of cells or tissues and causes many factors related to the pathogenesis of the disease.

Insulin resistance is one of the common risk factors for NAFLD and neurodegenerative diseases [14]. As a result of hepatic steatosis, hepatic insulin

resistance may develop. And peripheral insulin resistance leads to the development of brain insulin resistance. Brain insulin resistance and molecular disruption of IGF (insulin growth factor) receptors are sufficient to cause cognitive impairment and hippocampal degeneration with molecular abnormalities similar to AD [58]. Insulin resistance impairs cell viability, metabolism, and neuronal plasticity and increases oxidative stress, cytokine activation, and apoptosis. Therefore, regardless of the cause, hepatic insulin resistance plays a decisive role in the pathogenesis of hepatic steatosis and steatohepatitis.

Inflammation is a common feature of NAFLD patients. With the presence of NASH in NAFLD, inflammation is evident, spreads systemically and affects other organs, including the brain. Fatty infiltration of the liver and damage to hepatocytes stimulate the secretion of cytokines in NAFLD. Cytokines produced by macrophages promote the development of NASH. Systemic inflammation has been proposed as a cause of cognitive dysfunction in NAFLD and metabolic syndrome, and when inflammation affects the brain, cytokines and other pro-inflammatory factors are able to bypass blood-brain barrier (BBB) in a number of ways to disrupt brain function. In addition, cytokines can activate their receptors on peripheral endothelial cells, which promotes the release of inflammatory factors within the CNS [37]. These processes ultimately lead to the activation of microglia. Many experimental studies have shown evidence of a correlation between cognitive dysfunction and neuroinflammation in animal models of NASH [47]. Another study concluded that chronic inflammation originating outside the CNS (in the liver) is sufficient to induce AD-like symptoms even in the absence of genetic predisposing factors [17].

Neuroinflammation remains a focus of research in AD because it occurs early in the course of the disease and is mainly manifested by pro-inflammatory cytokines and microglial infiltration, especially near aggregates. Neuroinflammation contributes to AD pathology by promoting β-amyloid accumulation, Tau hyper-phosphorylation, oxidative damage, and impaired neuronal plasticity [58]. In addition, inflammation promotes insulin resistance and ceramide accumulation, i.e. increases lipotoxicity, contributing to neuronal damage and cholinergic dysfunction [59]. Cytokines are activated early in AD, and neuroinflammation may mediate neurodegeneration during early and possibly other selected stages of AD rather than throughout the course of the disease. Notably, a significant reduction in cytokine activation coincided with an increase in brain levels of β-amyloid, the end product of the phospho-Tau protein [58]. The activation of inflammatory pathways specific to NAFLD and NASH increases the production of some inflammatory mediators, such as IL-6, TNFα and IL-1β

cytokines. Furthermore, increased production of reactive oxygen species perpetuates the inflammatory cascade, which further increases IL-6 release, neuroinflammation, and neurodegeneration [42].

Ammonia levels are important in the pathogenesis of liver diseases. Hyperammonemia accelerates the development of NASH, exacerbates the inflammatory response, astrocyte swelling, and cognitive impairment. Hyperammonemia causes damage to neurons, disruption of synaptic plasticity. High levels of ammonia lead to mitochondrial dysfunction, increased activity of poly-ADF-ribose polymerase (an index of cell death) [1; 50]. In addition, hyperammonemia increases the secretion of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, and induces memory deficits in AD [1]. In AD, the large accumulation of β-amyloid alters the glutamate synthetase enzyme that detoxifies ammonia, resulting in increased ammonia levels leading to a neurotoxic state [55]. Therefore, elevated ammonia levels promote the progression to a more severe form of NAFLD, which then leads to memory loss and eventually dementia. Hyperammonemia also occurs in the simple steatosis stage of NAFLD. Studies show that the presence of long-term steatosis decreases gene expression of urea cycle enzymes and increases ammonia production [15; 16].

Recent evidence has shown a close relationship between changes in the intestinal microbiota and the development of NASH, which increases intestinal permeability to lipopolysaccharide (LPS), which activates TLR_4 of liver Kupffer cells and liver cells. The LPS-activated inflammatory cascade in the brain leads to a decrease in brain-derived neurotrophic factor (BDNF), decreases the number of viable cells in the pyramidal layer, and promotes neurodegeneration and atrophy of hippocampal neurons, thereby affecting CNS function, causing degenerative dementia and cognitive impairment. [46]. Gut microbiota helps regulate several metabolic and physiological homeostasis processes in the body, such as hormone secretion, gene expression, neurotransmitter secretion, and immune function. Gut dysbiosis leads to neurological disorders such as depression, anxiety and autism [52]. Numerous studies have demonstrated cognitive dysfunction and altered gut microbiota in patients with NAFLD. Finding the common microbiome species between NAFLD and Dementia may provide a basis for the development of therapies for the pathologies associated with these two diseases.

Dyslipidemia and disturbances in cholesterol metabolism are considered very important in the development of neurodegeneration in patients with NAFLD. Cholesterol is an important building block of the brain, which produces more than 20% of the total cholesterol in the body. High levels of cholesterol are essential for neuronal function. For this reason, neuronal cells have abundant cholesterol uptake

receptors such as low-density lipoprotein receptor (LDL), low-density lipoprotein receptor-related protein 1 (LRP1), and apoprotein-E (ApoE). Up to 70% of cholesterol in the brain is in the myelin sheath of oligodendrocytes and the membrane of astrocytes, and the rest is involved in the activity of neurons, including the formation of the myelin sheath of neurons that transmit synaptic signals. ApoE and LRP1 are associated with cholesterol metabolism and are important risk factors contributing to the prevalence of AD [17]. The ApoE4 variant increases the risk of AD and accelerates the onset of AD. LRP1 is an endocytic receptor highly expressed in the liver, neurons, vascular smooth muscle, and glial cells in the central nervous system, and is involved in the clearance of β-amyloid (Ab) from the central nervous system. Low-density lipoprotein receptor-related protein-1 (LRP1) is most abundantly expressed in the brain, liver, and lung. In the brain, it is highly expressed in glial cells, neurons, and cells of cerebral vessels. A significant decrease in LRP1 was observed in the central nervous system of WT and APP-Tg mice in FFA during chronic NAFLD [17]. This decline coincides with the earliest signs of AD. Decreased expression of LRP1 in chronic NAFLD may be the result of the loss of glial and neuronal cells, as these cells contain high amounts of LRP1. Alternatively, LRP1, which is involved in the clearance of Ab from the CNS, may be defective. Also, impaired Ab clearance was found in neurons of LRP1-deficient mice [23]. Binding of APP (β-amyloid precursor) to LRP1 leads to increased APP clearance. However, LRP1 is also involved in Ab production. Hence, its involvement in Ab synthesis and clearance makes it a key target in AD pathogenesis. It is hypothesized that ApoE Ab may inhibit or facilitate endocytosis of LRP1. LRP1, ApoE, or both are thought to be involved in the dysfunction of the lipid transport mechanism and Ab clearance (Figure 1). The LRP1 protein is a multifunctional receptor responsible for the absorption of dietary lipids by cells and the clearance of lipoproteins containing apolipoprotein E from the plasma. The protein also performs cellular regulatory functions by integrating multiple signal transduction events. Thus, the dysfunction of this receptor affects the development of a wide range of diseases, from cardiovascular diseases, obesity and diabetes to neurodegenerative diseases, tumor invasion and metastasis.

The main enzyme responsible for Ab production is β-secretase (BACE1), which is mainly found in the brain and may also be present in peripheral organs [41]. Under normal physiological conditions, Ab is produced to support synaptic plasticity and regulate the calcium influx required for synaptic communication transmission [33]. Clearance of Ab in the periphery is an important contributor to the development of AD, as insufficient clearance of Ab from the blood contributes

to Ab accumulation in the brain. Soluble Ab efflux through the BBB is hypothesized to be controlled by LRP1. LRP1 is understood as a mediator for Ab uptake by hepatocytes [41]. Theoretically, direct flow of Ab across the BBB for clearance by the liver would reduce Ab load in the brain, as 60% of brain-derived Ab is cleared by the periphery; however, insoluble Ab is a hallmark of AD pathology and cannot cross the BBB [41; 60]. The clearance of soluble Ab in the periphery is an important component of the development of AD, as insufficient clearance of Ab in the blood contributes to Ab accumulation in the brain [60]. One of the main functions of the liver is detoxification, which is important in the clearance of circulating Ab. A high concentration of Ab in the blood is observed as a result of a decrease in the ability of liver disease to detoxify. Hepatocytes can directly clear circulating Ab by uptake and degradation or by excretion. Ab uptake from the blood is carried out through lipoprotein receptor-related peptide 1 (LRP1) and low-density lipoprotein receptor (LDLR), which is abundant in hepatocytes [60]. Liver dysfunction and hepatic insulin resistance have been shown to inhibit the clearance of Ab from the blood by reducing the amount of LRP-1 in the liver and the translocation of LRP-1 to the hepatocyte membrane [62]. To counteract this effect, the use of treatments that enhance LRP1-mediated clearance of Ab by the liver improves cognition and mitigates the potentially deleterious effects of Ab within the brain. Thus, therapeutic intervention targeting the liver is emerging as a promising target for AD intervention and therapy.

Therefore, NAFLD is accompanied by a decrease in the liver of proteins involved in circulating Ab clearance (LRP1, LDLR) and Ab catabolism (insulin-degrading enzyme-IDE, neprilysin-NEP) [6; 43]. Impaired hepatic Ab degradation may contribute to increased circulating Ab, leading to increased Ab accumulation in the brain and the development of Alzheimer's disease [6; 18; 60]. The involvement of Ab, LRP1, and ApoE (especially the ApoE4 allele) in the pathogenesis of neurodegeneration and AD is complex and requires further investigation.

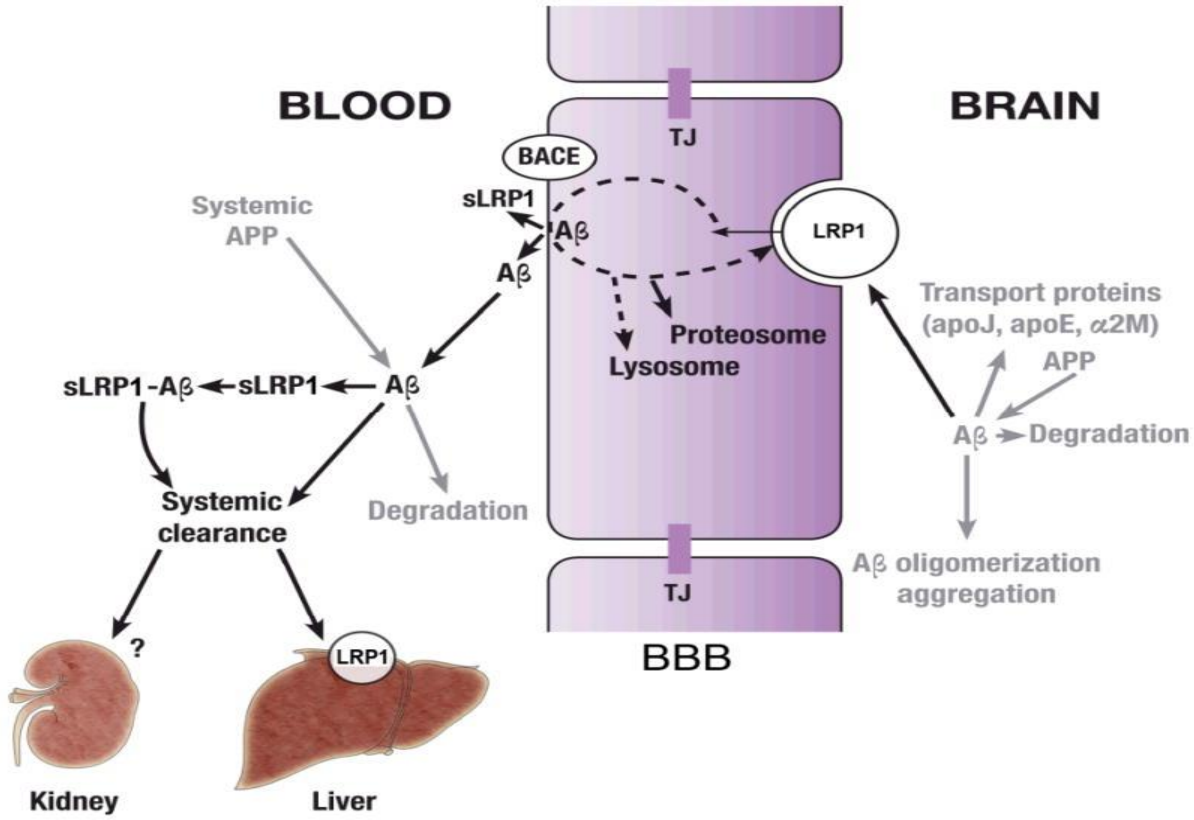

Figure 1. Involvement of the LRP1 receptor in the clearance of β-amyloid protein [7].

Also, according to the information presented in the literature, NAFLD damages the clearance of peripheral Ab in the liver and increases the conversion of cholesterol to 27-hydroxycholesterol, which allows peripheral cholesterol to enter the brain. Increased hydroxycholesterol influx into the brain induces brain oxidative stress and increases APP degradation. The resulting excess Ab is insufficiently removed from the brain by LRP1 due to impairments in BBB. Also, BBB impairment enhances the uptake of peripheral Ab by RAGE and increases the amount of Ab in the brain. Also, systemic inflammation caused by NAFLD disrupts BBB, resulting in Ab, 27-hydroxycholesterol, FFA, pro-inflammatory cytokines, and immune cells entering the brain from the blood. These factors affect the brain's immune and glial cells and their ability to clear and remove Ab, while increasing the amount of Ab precursors. In parallel, FFA and 27-GX disrupt the lipid content of neuronal cell membranes where the process of amyloidogenesis occurs, which increases the breakdown of APP into Ab. Accumulated Ab, however, is not adequately cleared from the brain by reduced LRP1. Activated glial and immune cells produce pro-inflammatory molecules such as TNF-α, IL-1β, IL-6, and iNOS, increasing neuroinflammation and triggering the development of neurodegeneration together with Ab accumulation [2].

When excess saturated fatty acids are incorporated into hepatocyte triglycerides, they cause lipotoxicity, resulting in liver damage. Lipotoxicity is a

state of cellular dysfunction caused by excessive accumulation of intracellular lipids, which activates oxidative stress and pro-inflammatory cytokines, increases the production of reactive oxygen species and toxic lipid intermediates, and inhibits β-oxidation. The role of fatty acids, sphingolipids and ceramides as mediators of lipotoxicity has been proposed. An excess of saturated fatty acids constitutes a preferential substrate for de novo ceramide biosynthesis. Ceramides and toxic lipids are thought to be important mediators of neurodegenerative diseases because these molecules are produced in liver, visceral fat, or brain tissue; may lead to insulin resistance [59]. Because AD is associated with an increase in blood sphingolipid, such as ceramide, it is hypothesized that ceramide released from the liver may target brain tissue via the blood and contribute to the development of AD. Dysregulation of ceramide metabolism, reflected by increased plasma ceramide levels, may occur at different stages of AD development [26]. Furthermore, it will be important to determine whether AD is associated with differential distribution of ceramides in lipoproteins but also in exosomes, which may be biomarkers of disease progression. Ceramides negatively alter cell functions and induce apoptosis by modulating the phosphorylation state of proteins, including insulin signaling proteins. In obesity, disturbances in sphingolipid metabolism in adipose tissue, skeletal muscle, and liver occur, leading to ceramide production, activation of inflammatory and anti-inflammatory cytokines, impaired glucose homeostasis, and impaired insulin responsiveness.

Given that toxic lipids (including ceramides) can cross the BBB and interfere with critical phosphorylation events, they can cause insulin resistance and serve as mediators of neurodegeneration by activating cytokines. Studies have also shown that ceramides produced or delivered outside the CNS can cause neuronal insulin resistance, neurodegeneration and neurocognitive deficits in the CNS [59].

Since ceramides are formed during myelin metabolism and degradation in the brain, local ceramide biosynthesis is increased under the influence of factors that disrupt oligodendroglial function. Locally increased ceramides have also been found to increase insulin resistance, neuroinflammation and oxidative stress in the brain [28]. The role of ceramides as a mediator of neurodegeneration may be related to the severity of steatohepatitis and the imbalance of lipid metabolism in the liver in the context of NASH. In general, many studies emphasize the role of the homocysteine-ceramide pathway in the pathology of Alzheimer's dementia [26].

Studies have shown that mRNA levels of several proceramide genes, including ceramide synthase (CerS), UDF-glucose ceramide glycosyltransferase (UGCG), serine palmitoyltransferase (SPTLC), and sphingomyelin

phosphodiesterase (SMase), are associated with neurodegeneration [45]. Sphingosine-1-phosphate (S1P) has been shown to be a potent regulator of NAFLD. A 2-fold increase in sphingosine kinase (SphK1) was also detected in mice fed a high saturated fat diet [12]. The liver is known to regulate plasma levels of S1P because the liver produces a chaperone, apolipoprotein M (apoM), to transport S1P. S1P secretion by hepatocytes may constitute a potent regulator of AD by targeting the brain. Therefore, the above results confirm that steatohepatitis causes insulin resistance, oxidative stress, and increased cytotoxic ceramides that exacerbate CNS damage, inflammation, and CNS damage.

In another study, the association between neurodegeneration and diet-induced NAFLD in juvenile pigs is explained by dysregulation of one-carbon metabolism [49]. Most of the choline in the brain comes from absorption in the small intestine and then passes through the BBB. Colonic excretion of choline-containing phospholipids as a result of increased rates of FFA and bile secretion is hypothesized to lead to depletion of choline and betaine in the brain, degradation of membrane phospholipids, and subsequent neuronal loss [25]. Studies show a link between NAFLD and neurodegeneration through increased synthesis of kynurenine, which can be converted into neurotoxic metabolites in the brain [9]. Inflammatory conditions in the liver and intestine inhibit indoleamine 2,3-dioxygenase (IDO-1), an intracellular enzyme that catalyzes the rate-limiting step in the conversion of tryptophan to kynurenine, possibly leading to liver damage and intestinal dysbiosis in kynurenine-tryptophan-fed pigs. ratio contributed to the growth of the frontal cortex of the brain. Also, short-chain fatty acids have been proven to have a negative effect on brain-related pathogenesis of NASH. An increase in the amount of bile acids in the brain is associated with neurodegenerative conditions in NAFLD. Primary conjugated bile acids are cytotoxic at high concentrations and can disrupt BBB [49].

Nervous system metabolism is directly dependent on the activity of SitC oxidase (SCO), a mitochondrial enzyme involved in ATF production. Research shows that in the NASH group, there is a decrease in SCO activity in the prefrontal cortex, hippocampus, thalamus and amygdala regions, which form part of the network underlying spatial working memory, and this decrease causes changes in the metabolic capacity of neurons. Brain mitochondrial dysfunction is one of the main drivers of neurodegeneration [31; 53]. Disruption of glucose metabolism in NASH has been found to affect neuronal circuits especially in the prefrontal area, because the density of excitatory synapses whose activity depends on the availability of glucose is high in the prefrontal cortex [43]. The activity of these prefrontal cortex excitatory synapses is related to dopamine because dopamine

modulates the impulse response of glutamatergic pyramidal neurons. A study found decreased levels of dopamine in the prefrontal cortex in NASH [53]. Dopaminergic dysfunction and decreased mitochondrial oxidative activity are observed due to insulin resistance and changes in monoamine oxidase and electron transport chain proteins.

Serum homocysteine (HCy) levels are elevated in NASH and are considered one of the early markers for the diagnosis of the disease [26]. Studies have shown that moderately elevated Hcy levels increase the risk of Alzheimer's disease [30]. A moderate increase in the amount of Hcy can increase the relative risk of dementia in the elderly by 1.15-2.5 times. Many experimental studies have shown that high levels of HCy cause many neurotoxic effects involving excitotoxicity, oxidative stress, mitochondrial dysfunction, DNA damage, and apoptosis, and hyperhomocysteinemia may be involved in neurodegeneration. Hyperhomocysteinemia increases Ab accumulation and tau hyperphosphorylation in brain Ab binding. Increased Hcy decreases S-adenosyl methionine (SAM) levels and blocks dimerization of apoE3, resulting in reduced apoE3-mediated formation of high-density lipoprotein (HDL) and microglial degradation of soluble Ab [44].

Many studies implicate the protein tyrosine-(Y)-phosphorylation-regulated kinase (DYRK1A) in AD. Increased levels of DYRK1A increase APP phosphorylation and cleavage, resulting in increased levels of Ab. Its direct stimulation of tau protein hyperphosphorylation indicates its involvement in neurodegenerative processes. In AD, plasma DYRK1A levels have been found to be positively correlated with cerebrospinal fluid Tau and phosphorylated-Tau proteins [8; 29].

Cognitive impairment in NAFLD may be associated with an imbalance of nesfatin-1 and copin-6 in the hippocampus and prefrontal cortex. Nesfatin-1 plays a role in mood and cognitive function in addition to regulating glucose and energy metabolism. Copin-6 participates in BDNF-related changes, regulates neurotransmission and promotes synaptic plasticity, learning and memory. Decreased levels of copin-6 are associated with depression-like behavior and have also been observed in NAFLD rats [11; 13].

In another study, increased levels of lipocalin2 (Lcn2) induced a strong induction of amphoterin ($HMGB_1$) in the liver and frontal cortex of the brain, which was associated with an increase in pro-inflammatory mediators in the brain, a subsequent decrease in the neurotrophic factor BDNF, and an increase in Tau protein depends [3]. As an adipokine, Lcn2 plays a role in various biological functions in the central nervous system. Lcn2 may act as a proapoptotic factor by sensitizing microglia to apoptotic stimuli. Lcn2 is thought to induce astrocytic

neurotoxicity. Notably, HMGB1 induces neuroinflammation by interacting with TLR_4 or RAGE receptors. Oxidative stress is increased in the brain in NASH after induction of $HMGB_1$ by Lcn2. Oxidative stress induces several inflammatory signaling pathways in NASH. Activation of p38 mitogen-activated protein kinase (MAPK) is one of the key intracellular signaling factors activated during oxidative stress. P38 MAPK activation has also been found to be involved in AD [34]. Notably, activated P38 MAPK contributes to the activation of nuclear factor kappa B (NF-κB), which is often responsible for the activation of Nod-like receptors (NLRP3), a key component of the inflammasome, and the secretion of cytokines and chemokines. NLRP3 activation with increased expression of caspase1, IL-6, IL-1β and IL-18 was found in the NASH model [3].

Another study reported that exposure to microcystin and a high-fat diet could induce NAFLD and significantly increase pro-inflammatory cytokine levels and increase Lcn2 and $HMGB_1$ in the frontal cortex of the brain. The above effects are due to the activation of the $NLRP_3$ inflammasome, as the use of $NLRP_3$ knockout mice abolished the increase in the inflammasome. $NLRP_3$ also causes a decrease in BBB tight junction proteins occludin and claudin 5. Increased blood S100β protein levels confirmed astrocyte activation and loss of BBB integrity in NAFLD. As a result, the protein levels of nitric oxide synthase (NOS), cyclooxygenase (COX-2) and Bax/Bcl_2 are increased in the frontal cortex, indicating oxidative stress-mediated neuronal cell apoptosis, which is crucial for neurodegeneration [4].

Recent studies have shown that a Western diet activates Na, K-ATPase signaling in the brain and peripheral tissues. The Na, K-ATPase signaling antagonist NaKtide (induced by doxycycline) ameliorated all effects of this diet, including cognitive memory decline and levels of BDNF, PSD95 (postsynaptic dense protein), Tau, phospho-Tau protein, and neurodegenerative o in the hippocampus restored the markers of change. These data suggest that western diet induces cognitive decline and neurodegeneration through activation of Na, K-ATPase signaling, and its antagonist ameliorates adipocyte pathophysiology and markers of neurodegeneration. If this observation is confirmed in humans, adipocyte Na, K-ATPase may serve as a clinical target for the treatment of neurodegenerative diseases [36].

Studies have shown that Ethanolamine plasmalogen (EtnPLA) phospholipids are reduced in metabolic disorders, including liver disease and Alzheimer's disease, and that PlsEtn produced in the liver plays a critical role in synaptic function in the brain [40]. Studies have shown that restoring or increasing PlsEtn levels by supplementing with PlsEtn or plasmalogen precursors can prevent metabolic and age-related diseases. Given that low-affinity neurotrophin receptor (p75NTR) Ab

plays an important role in the development of neuronal death, neurite degeneration, tau hyperphosphorylation, hepatic steatosis, studies have investigated the role of PlsEtn in steatohepatitis and memory impairment and its mechanism involved in correcting it by inhibiting p75NTR showed [64].

Therefore, currently, NAFLD is an important risk factor for the development of neurodegenerative diseases, and the pathophysiological pathways of brain dysfunction related to NAFLD are summarized as follows based on the above analysis (Fig. 2).

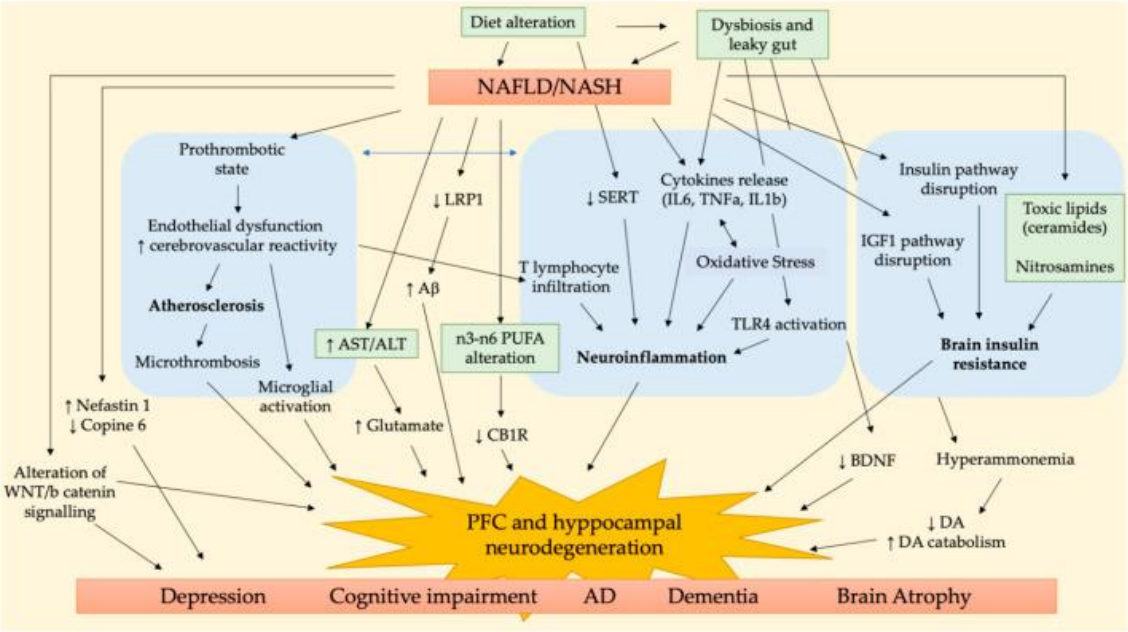

Figure 2. The main pathophysiological pathways of cognitive impairment in NAFLD [42]

Conclusion. In this review, we summarized the development of neurodegeneration based on insulin resistance, inflammation, hyperammonemia, intestinal dysbiosis, cerebrovascular dysfunction, etc., originating in NAFLD.

In conclusion, liver and metabolic dysfunction present even in the early stages of NAFLD contributes to the development of neurodegeneration and may place many patients at risk of developing dementia. Chronic inflammation induces liver-brain axis neurodegeneration due to decreased hepatic ceramide synthesis and hepatic Ab clearance, as well as common risk factors such as insulin resistance, obesity, etc.

In general, liver injury has a double-edged effect: inability of the injured liver to maintain peripheral Ab clearance increases Ab deposition in the brain. On the other hand, the release of pro-inflammatory cytokines by the damaged liver contributes to systemic inflammation, BBB disruption and subsequent neurodegenerative processes.

Therefore, chronic high-fat diet-induced NAFLD and its secondary neuroinflammation are sufficient to cause neurodegeneration, and we believe that this review is relevant to the millions of people at risk of developing AD or currently suffering from early signs of AD or dementia brings benefit. However, more research is needed to fully understand the mechanisms of functional changes resulting from high-fat diet-induced cognitive impairment.

REFERENCES

1. Adlimoghaddam A., Sabbir M.G., Albensi B.C. Ammonia as a Potential Neurotoxic Factor in Alzheimer's Disease // Front Mol Neurosci. –2016. –V.9. –P.57-59.

2. Angelika W., Anna M., Małgorzata W., Urszula W. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration // Ageing Research Reviews. –2021. 101397. https://doi.org/10.1016/j.arr.2021.101397.

3. Ayan M., Dipro B., Punnag S., Sutapa S., Ratanesh S., Diana K., Muayad A., Mitzi N., Prakash N., Saurabh Ch. Lipocalin 2 induces neuroinflammation and blood-brain barrier dysfunction through liver-brain axis in murine model of nonalcoholic steatohepatitis // Journal of Neuroinflammation. –2020. –V.17(201). https://doi.org/10.1186/s12974-020-01876-4.

4. Ayan M., Punnag S., Dipro B., Somdatta Ch., Ratanesh K. S., Shuo X., Dwayne E. P., Bryan W. B., Geoff I.S., Mitzi N., Prakash N., Saurabh Ch. Environmental Microcystin exposure in underlying NAFLD-induced exacerbation of neuroinflammation, blood-brain barrier dysfunction, and neurodegeneration are NLRP3 and S100B dependent // Toxicology. –2021. –V.461. 152901. https://doi.org/10.1016/j.tox.2021.152901.

5. Balzano T., Forteza J., Borreda I., Molina P., Giner J., Leone P., Urios A., Montoliu C., Felipo V. Histological Features of Cerebellar Neuropathology in Patients With Alcoholic and Nonalcoholic Steatohepatitis // J. Neuropathol. Exp. Neurol. –2018. –V.77. –P.837–845.

6. Bassendine M.F., Taylor-Robinson S.D., Fertleman M., Khan M., Neely D. Is Alzheimer's disease a liver disease of the brain? // J. Alzheimers Dis. –2020. –V.75. –P.1-14. https://doi.org/10.3233/jad-190848.

7. Berislav V. Z., Rashid D., Abhay P. S., Robert D. B., Ethan A.W. Low-density lipoprotein receptor-related protein-1 : a serial clearance homeostatic mechanism controlling Alzheimer's amyloid β-peptide elimination from the brain // J Neurochem. –2010. –V.115(5). –P.1077-1089. doi.org/10.1111/j.1471-4159.2010.07002.

8. Branca C., Shaw D.M., Belfiore R., Gokhale V., Shaw A.Y., Foley C. et al. Dyrk1 inhibition improves Alzheimer's disease-like pathology // Aging Cell. –2017. –V.16. –P.1146-1154. doi: 10.1111/acel.12648.

9. Breda C., Sathyasaikumar K.V., Sograte I.S., Notarangelo F.M., Estranero J.G., Moore G.G., Green E.W., Kyriacou C.P., Schwarcz R., Giorgini F. Tryptophan-2,3-dioxygenase (TDO) inhibition ameliorates neurodegeneration by modulation of kynurenine pathway metabolites // Proc Natl Acad Sci USA. –2016. –V.113. –P.5435-5440. doi:10.1073/pnas.1604453113.

10. Brian J., Angela K., Neville G., Ejaz A.Sh., Craig B., Kenneth H.F., Christopher G. Nonalcoholic Fatty Liver Disease in Patients with Inherited and Sporadic Motor Neuron Degeneration // Genes –2022. –V.13. –P.936. https://doi.org/10.3390/genes13060936.

11. Burk K., Ramachandran B., Ahmed S., Hurtado-Zavala J.I., Awasthi A., Benito E., Faram R., Ahmad H., Swaminathan A. McIlhinney J. et al. Regulation of Dendritic Spine Morphology in Hippocampal Neurons by Copine-6 // Cereb. Cortex. –2018. –V.28. –P.1087-1104.

12. Chen J., Wang W., Qi Y., Kaczorowski D., McCaughan G.W., Gamble J.R. et al. Deletion of sphingosine kinase 1 ameliorates hepatic steatosis in dietinduced obese mice: role of PPARγ // Biochim Biophys Acta. –2016. –V.1861. –P.138-47. doi:10.1016/j.bbalip.2015.11.006.

13. Chen Z., Xu Y.Y., Wu R., Han Y.X., Yu Y., Ge J.F., Chen F.H. Impaired learning and memory in rats induced by a high-fat diet: Involvement with the imbalance of nesfatin-1 abundance and copine 6 expression // J. Neuroendocr. –2017. –V.29.

14. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged // Arch Neurol. –2009. –V.66(3). –P.300–305.

15. De Ch.F., Heebol S., Marrone G., Montoliu C., Hamilton-Dutoit S., Ferrandez A., Andreola F., Rombouts K., Gronbaek H., Felipo V. Urea cycle dysregulation in non-alcoholic fatty liver disease // J. Hepatol. –2018. –V.69. –P.905–915.

16. De Chiara F., Thomsen K.L., Habtesion A., Jones H., Davies N., Gracia-Sancho J., Manicardi N., Hall A., Andreola F., Paish H.L. Ammonia Scavenging Prevents Progression of Fibrosis in Experimental Nonalcoholic Fatty Liver Disease // Hepatology. –2020. –V.71. –P.874–892.

17. Do-Geun K., Antje K., Leon E.T., Kirk J.M., Sudie-Ann R., Luisa T., Margaret S.B. Non-alcoholic fatty liver disease induces signs of Alzheimer's disease (AD) in wildtype mice and accelerates pathological signs of AD in an AD

model // Journal of Neuroinflammation. –2016. –V.13(1). doi10.1186/s12974-015-0467-5.

18. Estrada L.D., Ahumada P., Cabrera D., Arab J.P. Liver dysfunction as a novel player in Alzheimer's progression: looking outside the brain // Front. Aging Neurosci. –2019. –V.11. 174. https://doi.org/10.3389/fnagi.2019.00174.

19. Farrell G.C., Larter C.Z. Nonalcoholic fatty liver disease: From steatosis to cirrhosis // Hepatology. –2006. –V.43. –P.99–112.

20. Filipovic B., Markovic O., Đuric V., Filipovic B. Cognitive Changes and Brain Volume Reduction in Patients with Nonalcoholic Fatty Liver Disease // Can. J. Gastroenterol. Hepatol. –2018. 9638797.

21. G.S. Meghana., D.V. Gowda., S.B. Chidambaram., R.A. Osmani. Amyloid-β pathology in Alzheimer's disease: A nano delivery approach // Vibrational Spectroscopy.–2023.–V.126.103510. doi.org/10.1016/j.vibspec.2023.103510.

22. Gali C.C., Fanaee-Danesh E., Zandl-Lang M., Albrecher N.M., Tam-Amersdorfer C., Stracke A., Sachdev V., Reichmann F., Sun Y., Avdili A., Reiter M., Kratky D., Holzer P., Lass A., Kandimalla K.K., Panzenboeck U. Amyloid-beta impairs insulin signaling by accelerating autophagy-lysosomal degradation of LRP-1 and IR-β in blood-brain barrier endothelial cells in vitro and in 3XTg-AD mice // Mol. Cell. Neurosci. –2019. –V.99. 103390. https://doi.org/10.1016/j.mcn.2019.103390.

23. Goto J.J., Tanzi R.E. The role of the low-density lipoprotein receptor-related protein (LRP1) in Alzheimer's A beta generation: development of a cellbased model system // J Mol Neurosci. –2002. –V.19. –P.37–41.

24. Guimarães C.A., Biella M.S., Lopes A., Deroza P.F., Oliveira M.B., Macan T.P., Streck E.L., Ferreira G.C., Zugno A.I., Schuck P.F. In vivo and in vitro effects of fructose on rat brain acetylcholinesterase activity: An ontogenetic study // Acad. Bras. Cienc. –2014. –V.86. –P.1919–1926.

25. Hernandez G.V., Smith V.A., Melnyk M., Burd M.A., Sprayberry K.A., Edwards M.S., Peterson D.G., Bennet D.C., Fanter R.K., Columbus D.A., Steibel J.P., Glanz H., Immoos C., Rice M.S., Santiago-Rodriguez T.M., Blank J., VanderKelen J.J., Kitts C.L., Piccolo B.D., La Frano M.R., Burrin D.G., Maj M., Manjarin R. Dysregulated FXR-FGF19 signaling and choline metabolism are associated with gut dysbiosis and hyperplasia in a novel pig model of pediatric NASH // Am J Physiol Gastrointest Liver Physiol. –2020. –V.318. –P.582-609. doi:10.1152/ajpgi.00344.2019.

26. Hervé Le S., Julien V., Nadim K., Jessica D., Kelly M., Jean-Louis P., Céline C-G., Christophe M., Nathalie Janel. Deciphering the Link Between

Hyperhomocysteinemia and Ceramide Metabolism in Alzheimer-Type Neurodegeneration // Front. Neurol. –2019. –V10. https://doi.org/10.3389/fneur.2019.00807.

27. Higarza S.G., Arboleya S., Gueimonde M., Gómez-Lázaro E.; Arias J.L., Arias N. Neurobehavioral dysfunction in non-alcoholic steatohepatitis is associated with hyperammonemia, gut dysbiosis, and metabolic and functional brain regional deficits // PLoS ONE. –2019. –V.14. e0223019.

28. Holland W.L., Knotts T.A., Chavez J.A., Wang L.P., Hoehn K.L., Summers S.A. Lipid mediators of insulin resistance // Nutr Rev. –2007. –V.65. –P.39–46.

29. Janel N., Alexopoulos P., Badel A., Lamari F., Camproux A.C., Lagarde J. et al. Combined assessment of DYRK1A, BDNF and homocysteine levels as diagnostic marker for Alzheimer's disease // Transl Psychiatry. –2017. –V.7:e1154. doi:10.1038/tp.2017.123.

30. Janel N., Sarazin M., Corlier F., Corne H., de Souza L.C., Hamelin L. et al. Plasma DYRK1A as a novel risk factor for Alzheimer's disease // Transl Psychiatry. –2014. –V.4:e425. doi:10.1038/tp.2014.61.

31. Jha S.K., Jha N.K., Kumar D., Ambasta R.K, Kumar P. Linking mitochondrial dysfunction, metabolic syndrome and stress signaling in Neurodegeneration // Biochim Biophys Acta—Mol Basis Dis. –2017. –V.1863(5). –P.1132–1146. https://doi.org/10.1016/j.bbadis.2016.06.015.

32. Karbalaei R., Allahyari M., Rezaei-Tavirani M., Asadzadeh-Aghdaei H., Zali M.R. Protein-protein interaction analysis of Alzheimer`s disease and NAFLD based on systems biology methods unhide common ancestor pathways // Gastroenterol Hepatol Bed Bench. –2018. –V.11(1). –P.27–33.

33. Karisetty B. C., Bhatnagar A., Armour E. M., Beaver M., Zhang H., Elefant F. Amyloid-β peptide impact on synaptic function and neuroepigenetic gene control reveal new therapeutic strategies for Alzheimer's disease // Front. Mol. Neurosci. –2020. –V.13. 577622. https://doi.org/10.3389/fnmol.2020.577622.

34. Kheiri G., Dolatshahi M., Rahmani F., Rezaei N. Role of p38/MAPKs in Alzheimer's disease: implications for amyloid beta toxicity targeted therapy // Rev Neurosci. –2018. –V.30(1). –P.9-30.

35. Kim D.G., Krenz A., Toussaint L.E., Maurer K.J., Robinson S.A., Yan A., Torres L., Bynoe M.S. Non-alcoholic fatty liver disease induces signs of Alzheimer's disease (AD) in wild-type mice and accelerates pathological signs of AD in an AD model // J. Neuroinflamm. –2016. –V.13. –P.1.

36. Komal S., Rebecca P., Xiaoliang W., Hari V.L., Sneha S.P., Mishghan Z., Jiayan W., Lawrence G., Brandon H., James D., Jiang L., Sandrine P., Thomas

N., Joseph I.Sh. Role of adipocyte Na,K-ATPase oxidant amplification loop in cognitive decline and neurodegeneration // iScience. –2021. –V.24. 103262. http://creativecommons.org/licenses/by-nc-nd/4.0/.

37. Kristoffer K., Anne C.D.M., Charlotte W.W., Lea L.G., Peter L.E., Malene F.D., Rajeshwar P.M., Hendrik V., Mette M.L., Karen L.T. Cognitive Dysfunction in Non-Alcoholic Fatty Liver Disease—Current Knowledge, Mechanisms and Perspectives // J. Clin. Med. –2021. –V.10(673). https://doi.org/10.3390/jcm10040673.

38. Li X.Y., Zhang M., Xu W., Li J.Q., Cao X.P., Yu J.T., Tan L. Midlife modifiable risk factors for dementia: a systematic review and meta-analysis of 34 prospective cohort studies // Curr. Alzheimer Res. –2019. –V.16. –P.1254–1268. https://doi.org/10.2174/1567205017666200103111253.

39. Livingston G., Huntley J., Sommerlad A., Ames D., Ballard C., Banerjee S. Dementia prevention, intervention, and care: // 2020 report of the Lancet Commission. Lancet. –2020. –V.396(10248). –P.413–446.

40. M.A. Kling., D.B. Goodenowe., V. Senanayake., S. Mahmoudian Dehkordi., R. Baillie., X. Han. A. ethanolamine plasmalogens and phosphatide metabolism in the combined adni-1 go 2 cohort: does the liver contribute to ad risk by failing to supply key lipids to the brain// Alzheimer's Dement.–2018. –V.14. –P.998-999.

41. Marleigh H., Vineet B., Kailinn A., Daniela R., Vijay H. Cardiometabolic Modification of Amyloid Beta in Alzheimer's Disease Pathology // Front. Aging Neurosci. –2021. –V.13. https://doi.org/10.3389/fnagi.2021.721858.

42. Martina C., Daniela G., Sara De M. Depression and Cognitive Impairment-Extrahepatic Manifestations of NAFLD and NASH // Biomedicines. –2020. –V. 8(229). doi:10.3390/biomedicines8070229.

43. Meunier CNJ, Chameau P., Fossier P.M. Modulation of synaptic plasticity in the cortex needs to understand all the players // Front Synaptic Neurosci. –2017. –V.9(2). https://doi.org/10.3389/fnsyn.2017.00002.

44. Minagawa H., Watanabe A., Akatsu H., Adachi K., Ohtsuka C., Terayama Y. et al. Homocysteine, another risk factor for Alzheimer disease, impairs apolipoprotein E3 function // J Biol Chem. –2010. –V.285. –P.38382–38388. doi: 10.1074/jbc.M110.146258.

45. Ming T., Alexander N., Lisa L., Margot L., Jack R. Wands., Suzanne M. de la Monte. Nitrosamine Exposure Causes Insulin Resistance Diseases: Relevance to Type 2 Diabetes Mellitus, Non-Alcoholic Steatohepatitis, and Alzheimer's Disease // J Alzheimers Dis. –2009. –V.17(4). –P.827-844.

46. Mohammed S.K., Magdy Y.M., El-Waseef D.A., Nabih E.S., Hamouda M.A., El-Kharashi O.A. Modulation of hippocampal TLR4/BDNF signal pathway using probiotics is a step closer towards treating cognitive impairment in NASH model // Physiol. Behav. –2020. –V.214. –P.112762.

47. Mondal A., Bose D., Saha P., Sarkar S., Seth R., Kimono D., Albadrani M., Nagarkatti M., Nagarkatti P., Chatterjee S. Lipocalin 2 induces neuroinflammation and blood-brain barrier dysfunction through liver-brain axis in murine model of nonalcoholic steatohepatitis // J. Neuroinflammation. –2020. –V.17. –P.201.

48. Moroz N., Tong M., Longato L., Xu H., de la Monte S.M. Limited Alzheimer-type neurodegeneration in experimental obesity and Type 2 diabetes mellitus // J Alzheimers Dis. –2008. –V.15. –P.29–44.

49. Nicole Z., Isabell M., Gabriella V.H., Matthew J.T., Rob K.F., Mohammed A-I., Hunter G., Christine R.S., Douglas G.B., Michael R.La F., Rodrigo M., Magdalena M. Neurodegeneration in juvenile Iberian pigs with diet-induced nonalcoholic fatty liver disease // J Physiol Endocrinol Metab. –2020. –V.319. –P.592-606. doi:10.1152/ajpendo.00120.2020.

50. Oja S.S., Saransaari P., Korpi E.R. Neurotoxicity of Ammonia // Neurochem Res. –2017. –V.42(3). –P.713–20.

51. Pinçon A., De Montgolfier O., Akkoyunlu N., Daneault C., Pouliot P., Villeneuve L., Lesage F., Levy B.I., Thorin-Trescases N., Thorin É.. Non-Alcoholic Fatty Liver Disease, and the Underlying Altered Fatty Acid Metabolism, Reveals Brain Hypoperfusion and Contributes to the Cognitive Decline in APP/PS1 Mice // Metabolites. –2019. –V.9. –P.104.

52. Rogers G.B., Keating D.J., Young R.L., Wong M.L., Licinio J., Wesselingh S. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways // Mol Psychiatry. –2016. –V.21(6). –P.738-748.

53. Sara G.H., Silvia A., Miguel G., Eneritz G-L., Jorge L.A., Natalia A. Neurobehavioral dysfunction in non-alcoholic steatohepatitis is associated with hyperammonemia, gut dysbiosis, and metabolic and functional brain regional deficits // PLOS ONE. –2019. https://doi.org/10.1371/journal.pone.0223019.

54. Shang Y., Nasr P., Ekstedt M., Widman L., Stal P., Hultcrantz R. Non-alcoholic fatty liver disease does not increase dementia risk although histology data might improve risk prediction // JHEP Rep. –2021. –V.3(2).100218.

55. So Yeong Cheon., Juhyun Song. Novel insights into non-alcoholic fatty liver disease and dementia: insulin resistance, hyperammonemia, gut dysbiosis, vascular impairment, and infammation // Cheon and Song Cell & Bioscience - 2022. –V.12. –P.1-14. https://doi.org/10.1186/s13578-022-00836-0.

56. Solfrizzi V., Scafato E., Custodero C., Loparco F., Ciavarella A., Panza F., Seripa D., Imbimbo B.P., Lozupone M., Napoli N. Liver fibrosis score, physical frailty, and the risk of dementia in older adults: The Italian Longitudinal Study on Aging //Alzheimers Dement. –2020. –V.6. e12065.

57. Sun Z., Wang Z.T., Sun F.R., Shen X.N., Xu W., Ma Y.H., Dong Q., Tan L., Yu J.T. Late-life obesity is a protective factor for prodromal Alzheimer's disease: a longitudinal study // Aging (Albany. NY). –2020. –V.12. –P.2005–2017. https://doi.org/10.18632/aging.

58. Suzanne M. de la Monte, Ming Tong. Brain metabolic dysfunction at the core of Alzheimer's disease // Biochem Pharmacol. –2014. –V.88(4): –P.548–559. doi:10.1016/j.bcp.2013.12.012.

59. Suzanne M., Lisa Longato., Ming Tong. Jack R Wands. Insulin resistance and neurodegeneration: Roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis // Curr Opin Investig Drugs. –2009. –V.10(10). –P.1049–1060.

60. Van D.C.H. Anti-amyloid-β monoclonal antibodies for Alzheimer's disease: pitfalls and promise // Biol. Psychiatry –2018. –V.83. –P.311–319. https://doi.org/10.1016/j.biopsych.2017.08.010.

61. Vonghia L., Michielsen P., Francque S. Immunological mechanisms in the pathophysiology of non-alcoholic steatohepatitis // Int. J. Mol. Sci. -2013. –V.14. –P.19867–19890.

62. Wang, Y.R., Wang Q.H., Zhang T., Liu Y.H., Yao X.Q., Zeng F., Li J., Zhou F.Y., Wang L., Yan J.C. et al. Associations Between Hepatic Functions and Plasma Amyloid-Beta Levels—Implications for the Capacity of Liver in Peripheral Amyloid-Beta Clearance. Mol. Neurobiol. 2017, 54, 2338–2344.

63. Xu T., Zhou J., Zhu J., Zhang S., Zhang N., Zhao Y. Carnosic acid protects non-alcoholic fatty liver-induced dopaminergic neuron injury in rats // Metab Brain Dis. –2017. –V.32(2). –P.483-491.

64. Yanjun L., Peixu C., Tao Zh., Rui W., Xiaoxu W., Junyi L., Xinceng W., Jie Xu., Yuming W., Jingfeng W., Changhu Xue. Plasmalogen attenuates the development of hepatic steatosis and cognitive deficit through mechanism involving p75NTR inhibition // Redox Biology. –2021. –V.43. 102002. https://doi.org/10.1016/j.redox.2021.102002.

65. Zeltser N., Meyer I., Hernandez G.V., Trahan M.J., Fanter R.K., Abo-Ismail M. Neurodegeneration in juvenile Iberian pigs with diet-induced nonalcoholic fatty liver disease // Am J Physiol Endocrinol Metab. –2020. –V.319(3). –P.592-606.

66. A.A. Basalay, T.Ye. Kuznetsova, T.A. Mityukova, O.Ye. Polulyakh, Ye.N. Chudilovskaya, N.S. Kostyuchenko, YA.V. Shcherbakov, T.A. Khrustalova, S.V. Gubkin. Morfofunktsional'noye sostoyaniye pecheni krys-samtsov linii vistar pri diyet-indutsirovannom ozhirenii i yego korrektsii // Proceedings of the National Academy of Sciences of Belarus. Medical series. -2022. –V.19(3). -P.308–320. A.A. Basalai, T.E. Kuznetsova, T.A. Mityukova, O.E. Polulyakh, E.N. Chudilovskaya, N.S. Kostyuchenko, Ya.V. Shcherbakov, T.A. Khrustaleva, S.V. Gubkin. Morphofunctional state of the liver of male Wistar rats with diet-induced obesity and its correction // Proceedings of the National Academy of Sciences of Belarus. medical series. -2022. –V.19(3). -P.308–320.

67. R.V. Yanko, Ye.G. Chaka, A.S. Zinchenko, S.L. Safonov, M.I. Levashov. Osobennosti modelirovaniya zhirovogo gepatoza u krys raznogo vozrasta na osnove vysokokaloriynogo ratsiona // Ozhireniye i metabolizm. – 2021. – T. 18. – №4. – S. 387-397. R.V. Yanko, E.G. Chaka, A.S. Zinchenko, S.L. Safonov, M.I. Levashov. Features of modeling fatty hepatosis in rats of different ages based on a high-calorie diet // Obesity and metabolism. - 2021. - T. 18. - No. 4. – pp. 387-397.