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Research Progress of Lipid Droplets in the Regulation of Lipid Metabolism Function in the Central Nervous System

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Abstract: Lipid droplet is an organelle closely related to lipid metabolism, storing intracellular neutral lipids such as triglycerides (TAGs) and cholesterol esters (CEs) in the case of excess fatty acids. A growing number of studies have identified abnormal accumulation of lipid droplets in nerve cells during early development, aging, and neuropathy. In this review, from the perspective of lipid droplet, we first clarified the metabolism of lipid in the brain and the physiological function of lipid droplet in the central nervous system, then summarized the regulatory mechanism between lipid droplet and nerve cells in the central nervous system, and finally studied the relationship between abnormal lipid droplet metabolism and the occurrence of central nervous system diseases.

1. Introduction

The health and function of the nervous system are closely related to lipid homeostasis. The brain is composed of nearly 50% dry weight lipids, making it the second largest lipid tissue in the human body after adipose tissue [9]. Lipid droplets (LDs) are organelles that store intracellular neutral lipids, such as triacylglycerols (TAGs) and cholesteryl esters (CEs). This storage is crucial for the timely release of fatty acids required for cell signaling, lipid synthesis, and energy production [26]. Therefore, dysregulation or excessive accumulation of lipid droplets can lead to central nervous system dysfunction. In recent years, lipid droplets have received increasing attention in the pathologies of obesity, insulin resistance, type 2 diabetes, hepatic steatosis, cardiovascular diseases, etc., but their role in the regulation of lipid metabolism in the central nervous system remains to be clarified. This article will review the progress in the role of lipid droplets in the regulation of lipid metabolism in the central nervous system, thereby providing a reference for subsequent research.

2. Lipid Metabolism in the Brain

Brain lipids consist of 50% phospholipids, less than 40% glycolipids, 10% cholesterol, cholesterol esters, and trace amounts of triacylglycerols. Lipid droplets (LDs) are mainly found in the cytoplasm of eukaryotic cells and are composed of neutral lipids (such as triacylglycerols (TAGs) and cholesteryl esters (CEs)) and a monolayer of phospholipids [9]. In eukaryotes, lipid droplets are generated on the endoplasmic reticulum through a series of steps: first, neutral lipids

are synthesized, most commonly triacylglycerols and sterol esters. They are produced by the esterification of activated fatty acids to diacylglycerols or sterols (such as cholesterol). Then, oil lenses are formed, and as the concentration of neutral lipids increases, they eventually combine and form oil lenses during the separation process. Next, the neutral lipid lenses expand and bud from the endoplasmic reticulum membrane to form nascent lipid droplets. Finally, lipid droplets fuse, grow, and mature [20,28].

There are two main mechanisms for the transformation of lipid droplets: lipolysis and lipophagy. One is lipolysis, where lipases directly bind to the surface of lipid droplets and catalyze the continuous hydrolysis of triacylglycerols into free fatty acids and glycerol. The second mechanism of lipid droplet metabolism is lipid droplet-specific autophagy or lipophagy. Lipophagy is a selective autophagy targeting lipid droplets and plays an important regulatory role in the degradation and accumulation of lipid droplets in other cells. After being engulfed by autophagosomes, lipid droplets fuse with lysosomes containing lysosomal acid hydrolases, and the lysosomes hydrolyze triacylglycerols [14].

Lipid droplets are highly dynamic and actively participate in cellular lipid accumulation, storage, and metabolism. The dysregulation of lipid synthesis and metabolism in the brain may be a new biological mechanism affecting the progression of central nervous system diseases.

3. Functions and Roles of Lipid Droplets in the Central Nervous System

The formation of lipid droplets has many effects on cell physiology. The neutral lipids stored in lipid droplets can be used in physiological processes such as synaptic formation, cell membrane synthesis, and energy metabolism. The presynaptic protein Mover/TPRG1L (Mossy fiber associated vertebrate-specific protein; also called TPRG1L) is a component of the lipid droplet shell in astrocytes and can regulate neurotransmitter release in neurons, which may be closely related to lipid-related neurological diseases [12]. Additionally, TREM2 (triggering receptor expressed on myeloid cells 2)-dependent lipid droplet generation is necessary for myelin regeneration [7].

Previous studies have confirmed that another function of lipid droplet formation is to protect cells from lipid peroxidation. Lipid accumulation induced by oxidative stress is mediated by lipid droplet homeostasis, which isolates unsaturated triglycerides in lipid droplets to prevent further peroxidation. The final step of triglyceride synthesis is regulated by two diacylglycerol acyltransferases (DGAT1 and DGAT2). Studies have found that an increase in DGAT1 levels can store excess fatty acids (FAs) in triglycerides and lipid droplets. Inhibiting DGAT1 disrupts lipid homeostasis, leading to excessive FAs entering mitochondria for oxidation, resulting in high levels of reactive oxygen species (ROS) production, mitochondrial damage, cytochrome c release, and apoptosis [6]. Lipopolysaccharide-binding protein (LBP) protects long-chain unsaturated triglycerides rather than saturated triglycerides from entering lipid droplets, thereby inducing lipid accumulation. In this study, it was also demonstrated that LBP is connected to lipid metabolism and redox signaling pathways, precisely maintaining intracellular homeostasis to adapt to oxidative stress [29]. Additionally, studies have shown that the activation of the Wnt signaling pathway plays a crucial role in regulating lipid homeostasis by enhancing lipolysis while inhibiting lipogenesis and fatty acid β-oxidation [17]. Molecular hydrogen (H2) has the ability to neutralize cytotoxic ROS and protect cellular structures from oxidative stress damage. Research has found that hydrogen-rich water enhances cellular lipid metabolism and promotes the degradation of lipid droplets by activating the AMPK/Nrf2/HO-1 pathway, thereby reducing the diameter of lipid droplets, lowering lipid peroxidation, and reducing fatty acid-induced oxidative stress [24]. This study provides a basis for the use of molecular hydrogen in the treatment of brain diseases, but the specific mechanism still requires further research.

Inflammatory responses are one of the key functions of astrocytes and microglia, and are associated with the upregulation of genes related to lipid storage functions [1]. Studies have confirmed that lipid droplets are crucial for maintaining the anti-inflammatory properties of microglia. A specific adipose triglyceride lipase (ATGL) inhibitor, atglistatin, has been shown to prevent the production of pro-inflammatory cytokines in primary microglia by reducing lipid droplet lipolysis [13]. Moreover, lipid droplet biogenesis is associated with the innate immune response of microglia induced by cerebral ischemia. Aging microglia accumulate lipids in a stable state and exhibit an exacerbated innate immune response to stroke [2]. However, in another study, it was found that in the hippocampus of aged mice, microglia present a new state - excessive lipid droplet accumulation, and microglia with lipid droplet accumulation are in an activated state, capable of generating high levels of ROS and releasing pro-inflammatory factors such as IL-6, IL-1α, IL-1β, and TNF-α. These lipid droplet-accumulating microglia (LDAM) exhibit a dysfunctional and pro-inflammatory state [18].

These research results suggest that under physiological conditions, lipid droplets, as organelles for storing neutral lipids, are crucial for maintaining brain homeostasis. Lipid droplets are involved in various physiological processes in the central nervous system, such as neurotransmission, myelination, and cell membrane synthesis. Additionally, lipid droplets play a protective role against various stressors and prevent lipotoxicity. Disorders of lipid droplet metabolism may cause lipid peroxidation and inflammatory responses, which in turn damage the brain and lead to central nervous system diseases. Whether lipid droplets are the result or the cause of inflammation, or whether they interact with each other, remains to be determined.

4. Regulatory Roles of Lipid Droplets among Different Neuronal Cells in the Central Nervous System

When the brain is in a pathological state, abnormal accumulation of lipid droplets can be observed in various types of neuronal cells, such as neurons, microglia, and astrocytes [21]. Do lipid droplets interact among different neuronal cells? And how do they function?

4.1 Microglia and Neurons

Recent studies have shown that there is a close connection between microglia and neurons, and microglia can actively regulate neuronal activity [3,19]. Lipid transporters play a role in the metabolic homeostasis of the nervous system, especially apolipoprotein E (ApoE)[27]. APOE4 induces an activated state in microglia, accumulating intracellular neutral lipids by reducing the uptake of extracellular fatty acids and lipoproteins, forming lipid droplets. Additionally, this alteration in the lipid accumulation state disrupts microglial homeostasis and impairs mitochondrial function, which may inhibit neuronal firing [25]. Neuronal mitochondrial metabolism is crucial for activity-dependent calcium buffering, synaptic transmission, and action potential generation [8]. In another study, it was found that neuronal AMPK (AMP-activated protein kinase, AMPK) can regulate the accumulation of lipid droplets in microglia in the brain. Neurons with tau disease transfer lipids to glial cells through mediators, leading to lipid droplet accumulation and inflammation in microglia. At the same time, neuronal AMPK inhibits lipogenesis and promotes neuronal lipophagy, thereby reducing lipid flow to microglia [15].

4.2 Astrocytes and Neurons

Astrocytes support neurons in the following ways: they provide energy through the astrocyte-neuron lactate shuttle, protect neurons from excitotoxicity, internalize neuronal lipid

droplets to degrade fatty acids to support neuronal metabolism and synapses, and through their high glutamate uptake and conversion of glutamate to glutamine. Under oxidative stress, neurons transfer lipids to lipid droplets in astrocytes via apolipoproteins to prevent fatty acid toxicity, and this transport mechanism is dependent on ApoE subtypes [5,11]. Studies have shown that ApoE4 plays an important role in mediating the transfer of fatty acids from neurons to astrocytes [22]. Astrocytes release free fatty acids from lipid droplets into mitochondria to form long-chain acylcarnitines, causing mitochondrial damage and reducing astrocyte metabolic support, thereby exacerbating neuronal damage [10]. In a high-fat environment, the mitochondrial and lysosomal functions of astrocytes may be disrupted, and this disruption may potentially hinder the supportive role of astrocytes in neuronal function [16].

4.3 Microglia and Astrocytes

Activated microglia express higher levels of Ch25h, an enzyme that hydroxylates cholesterol to produce 25-hydroxycholesterol (25HC). 25HC plays an important role in regulating astrocyte lipid metabolism. This study found that after treating astrocytes with 25HC, the level of extracellular ApoE increased, and the promoting effect of 25HC on extracellular ApoE3 was better than that on ApoE4. The increase in extracellular ApoE is due to the enhanced efflux caused by the upregulation of the lipid transport protein ABC protein family (ATP-binding cassette transporter A1, Abca1) through liver X receptors (LXRs), as well as the reduced lipoprotein reuptake resulting from the inhibition of low-density lipoprotein receptor (LDL-R) expression by suppressing sterol regulatory element-binding proteins (SREBPs). 25HC also inhibits the expression of sterol regulatory element binding factor 2 (Srebf2), but not Srebf1, leading to a reduction in cholesterol synthesis in astrocytes without affecting fatty acid levels. Further studies have shown that 25HC promotes the activity of sterol-O-acyltransferase, doubling the amount of cholesterol esters and their storage in lipid droplets [4].

In summary, lipid droplets, neurons, microglia, and astrocytes are closely related and jointly regulate lipid homeostasis in the brain. ApoE, especially ApoE4, plays a crucial role in the communication between astrocytes and neurons, as well as between microglia and neurons.

5. Abnormal Lipid Droplet Metabolism and the Occurrence of Central Nervous Diseases

5.1 Alzheimer's Disease

Alzheimer's disease is the world within the scope of the most common neurodegenerative disease, excessive phosphorylated tau protein and A beta patch is considered to be the Alzheimer's disease (Alzheimer diseases, AD) two pathological features. Several genetic risk factors of AD are related to genes associated with lipid metabolism, many of which are highly expressed in glial cells. Recent studies have confirmed that the accumulation of cholesterol within cells can impair the clearance function of defective mitochondria, which may be one of the pathogenic mechanisms of AD. A large number of studies have shown that the E4 variant of APOE is closely related to Alzheimer's disease. APOE is transported to astrocyte lipid droplets and regulates triglyceride saturation and droplet size. APOE4 astrocytes have large, unsaturated low-density regions and are sensitive to lipid peroxidation reaction. Further research has found that A microglial cell state defined by the expression of AcylCoA synthetase long-chain family member 1 (ACSL1), a lipid droplet-associated enzyme, Among them, ACSL1-positive microglia were most abundant in patients with Alzheimer's disease of the APOE4/4 genotype. More and more research evidence indicates that lipid droplets and lipid droplet homeostasis balance play a key role in Alzheimer's disease, but the specific pathogenesis in the disease still needs further study.

5.2 Parkinson's Disease

Parkinson's disease, PD is the most common type of synaptic nucleoprotein, neurons protein alpha-synuclein (alpha synuclein, alpha S) and the accumulation of lipid metabolic abnormalities are associated with the pathogenesis of Parkinson's disease. Studies have found that in the neuronal model of synucleinopathy, the activated retinol-X-receptor (RXR) can regulate fatty acid desaturase to varying degrees and stimulate lysosomes to clear αS, thereby regulating fatty acid metabolism and αS turnover. In another study, it was found that reducing hormone sensitive lipase LIPE (hsl) in mice with α -synuclein mutations could improve Parkinson-like defects and reveal gender differences in fatty acid metabolism. LIPE has the potential to become a promising target for male Parkinson's disease. All the above studies suggest that fatty acid turnover is a therapeutic target for Parkinson's disease. At present, there is still no effective treatment plan to prevent or slow down the loss of neurons or the progression of related symptoms in Parkinson's disease. However, in a recent study, it was found that linoleic acid, as a fatty acid, has effective neuroprotective and anti-inflammatory antioxidant effects on Parkinson's disease both in vitro and in vivo.

5.3 Ischemic Stroke in Acute

Ischemic stroke (Acute ischemic stroke, AIS) is a worldwide one of the leading causes of disability and death. Studies have found that lipid droplets are generated in brain endothelial cells after ischemic stroke [1]. The trigger receptor (TREM2) expressed on bone marrow cell 2 is a transmembrane receptor protein, which is mainly expressed in microglia within the central nervous system. The research by Wei W et al. confirmed that TREM2 can alleviate neuroinflammation induced by stroke by regulating the TGF-β1/Smad2/3 signaling pathway. TREM2 is highly expressed in microglia activated after ischemic stroke. Knockout of TREM2 leads to an increase in lipid droplet formation and lipid synthesis after hypoxia, and a decrease in cholesterol clearance and lipid hydrolysis, further affecting the microglial phenotype and promoting the transformation of microglial cells to an inflammatory phenotype [23]. In addition, it was determined through lipidomics analysis that long-chain acylcarnitine is the target of ischemic stroke. LCAC accumulates and damages neurons by inducing mitochondrial dysfunction in astrocytes of AIS cells [16]. The above results indicate that lipid metabolism dysfunction is widely involved in the pathological process of ischemic stroke, and lipid droplets have received increasing attention in Parkinson's disease.

6. Conclusions

With the deepening of the research level, people are constantly improving on the structure and function of lipid drops, synthesis and degradation process of understanding, clear the lipid drops in various nerve cells in the pathophysiological mechanisms, and they play a role in diseases of the central nervous system. However, there are still some problems, such as: Are lipid droplets the result or cause of neuroinflammation and oxidative stress? Or perhaps they interact with each other? Therefore, more research is still needed in the future to explore the mechanism of lipid droplets in the regulation of lipid metabolism function in the central nervous system.

Author Contributions

Huiqun He conceptualized the study. Huiqun He, YuMei Ren, Xinwen Zhang contributed to the reading, outlining, drafting, reviewing and incorporating relevant corrections into the text. Xinwen Zhang contributed to the funding acquisition.

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