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Lipid Metabolism in Neuroglia and Its Role in Brain Development and Dysfunction

Wen Wang[1,a], Huiqun He[1,b], Yumei Ren[1,c], Xinwen Zhang[2,d,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]Xi'an People's Hospital/Xi'an Fourth Hospital, Xi'an, Shaanxi, 710004, China
[a]1093891987@qq.com, [b]17889775532@163.com, [c]2812450466@qq.com, [d]xianxinwen@163.com
**Corresponding author*

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Abstract: neuroglia undertakes a variety of crucial physiological functions in the nervous system, encompassing neural support, myelin formation, immune responses, etc. Research in recent years indicates that neuroglia are not only closely associated with the functions of neurons but also play a key role in lipid metabolism. Lipids such as fatty acids, cholesterol, and phospholipids, along with lipid metabolites, not only constitute the basis for the normal functions of neuroglia but also are involved in brain development, brain functions, and the occurrence of various neurological disorders. Hence, this article summarizes the fundamental functions of neuroglia and the role of their lipid metabolism in brain development and neurological diseases, and discusses the potential influence of lipid metabolic disorders in neuroglia on brain functions.

1. Introduction

The brain of mammals is a complex organ composed of neurons, glial cells and synapses. Glial cells are the most numerous type of cells in the central nervous system (CNS) of mammals, accounting for approximately 50% of all neural cells, mainly including microglia, astrocytes and oligodendrocytes, etc. [1]. Unlike neurons, glial cells do not directly participate in signal transmission, but they can transmit signals and exchange substances through the mechanism of extracellular vesicle transport [2]. These cells play a crucial role in brain development, especially in the development of brain nerves, the formation and maintenance of the blood-brain barrier, neural plasticity and memory formation. In addition, glial cells ensure the normal physiological functions of neurons by regulating neurotransmitters, maintaining ion concentration balance and removing metabolic wastes.

Lipids, as the basic components of cell membranes, play a significant role in human health and the normal function of the nervous system. The brain is rich in lipids, with the weight of brain lipids accounting for at least half of the brain's dry weight. The content of brain lipids is second only to that of adipose tissue. Lipids are the basic structural components of neuronal cell membranes and the main building blocks of myelin. The structure and function of the brain are highly dependent on lipids, including phospholipids, sphingolipids and cholesterol, etc. [3]. Glial cells regulate lipid metabolism in multiple ways, and the disorder of lipid metabolism can also lead to glial cell dysfunction, thereby affecting the development and function of the nervous system, and further causing various

neurodegenerative diseases and neurodevelopmental disorders [4].

2. The Functions of Glial Cells

2.1 Microglia

As the unique innate immune cells in the central nervous system, microglia are involved in the immune defense and surveillance of the nervous system. They have the ability to recognize and eliminate pathogens, damaged cells, and cell debris, and can release cytokines to activate immune responses and clear pathogens [5]. When the brain is in a pathological state, the microenvironment is affected and changes, rapidly activating microglia to transform into pro-inflammatory M1 or anti-inflammatory M2 types. M1-type microglia can release various pro-inflammatory factors, leading to cytotoxicity and acute immune responses; M2-type microglia, on the other hand, secrete anti-inflammatory factors and growth factors to suppress inflammation and immune responses, providing protection for the central nervous system. Unsaturated fatty acids can promote the polarization of microglia and inhibit inflammatory signals. Docosahexaenoic acid (DHA), a typical omega-3 fatty acid, protects neurons by influencing the expression of apolipoprotein E (ApoE), reducing the risk of sporadic Alzheimer's disease [6]. Microglia also participate in the modification of dendritic spines, enhancing synaptic plasticity. They can detect damaged or dead neurons, phagocytize and clear cell debris, participate in synaptic pruning and neural circuit development, and also provide a favorable microenvironment for neural repair [7].

2.2 Astrocytes

Astrocytes can regulate immune responses and maintain the blood-brain barrier [8]. Their surfaces are rich in protrusions that can closely contact capillaries to absorb various nutrients such as glucose and amino acids from the blood and transport them to the vicinity of neurons, serving as raw materials for energy supply and protein synthesis. They can also secrete a large amount of neurotrophic factors and substances that support neurons. These factors and substances not only provide nutrition for neurons but also promote their survival and development. Besides transporting glucose to neurons, astrocytes are the only cells in the brain that can oxidize fatty acids and produce ketone bodies to provide energy for neurons in a hypoglycemic or fasting state [9]. As specialized immune cells in the brain, astrocytes also have the function of antigen presentation, can induce the proliferation and differentiation of microglia, and interact with microglia. Both secrete cytokines and interact through paracrine signaling to jointly regulate immune responses and neuroinflammation [10]. In addition, astrocytes are an important component of tripartite synapses, and there is bidirectional communication between neurons and astrocytes, which maintains homeostasis and neuronal survival. Culturing neurons without astrocytes leads to neuronal degeneration and eventual death. Experiments using pure neuronal cultures have shown that astrocytes can actively promote the formation of new synapses. After receiving signals from neurons, astrocytes induce the release of neurotransmitters that bind to synaptic receptors, thereby regulating the transmission of neural signals between synapses. The phagocytic activity of astrocytes is particularly important for maintaining normal hippocampal synaptic connections and synaptic plasticity [11].

2.3 Oligodendrocytes

Oligodendrocytes surround the axons of nerve fibers in the central nervous system to form myelin sheaths, providing an efficient and rapid channel for the rapid conduction of neural signals [12]. Myelin is rich in lipids and has a unique lipid composition ratio. 70% of the cholesterol in the human

body is found in myelin membranes. The ratio of cholesterol, phospholipids, and glycolipids in most biological membranes is 25%:65%:10%, while the lipid composition ratio of myelin is 40%:40%:20% [13]. Due to the function of the blood-brain barrier, the central nervous system can hardly utilize cholesterol in the circulation. Oligodendrocytes preferentially use ketone bodies as raw materials to synthesize cholesterol through de novo pathways. In the central nervous system, the transport of cholesterol is accomplished by special lipoproteins secreted by astrocytes, such as apolipoprotein E (ApoE) [14]. However, only mature oligodendrocytes can form myelin sheaths. During the proliferation and differentiation of oligodendrocyte precursor cells into mature oligodendrocytes, microglia are also involved. Microglia can regulate myelin formation by secreting insulin-like growth factor-1 [15, 16]. Oligodendrocytes can also influence the development and survival of neurons, astrocytes, and even themselves by secreting neurotrophic factors and nerve growth factors [17].

3. Glial Cell Lipid Metabolism Disorders and Brain Development and Dysfunction

3.1 The Role of Lipids in Brain Development

Lipids are one of the seven essential nutrients for the human body, and the organ with the highest lipid content in the human body is the brain [18]. The lipids in the brain are mainly sphingolipids and cholesterol, which play a very important role in brain development and function maintenance. Cholesterol is the most important component and basic functional unit of the cell membrane in mammals and is also necessary for cell processes such as glial cell proliferation, neurite growth, microtubule stability, synaptogenesis, and myelination [15]. Sphingolipids are important structural components of the plasma membrane and are involved in neuronal differentiation, synaptic transmission, and neuron-glia cell connections. They are also related to myelin stability and regulate cell growth, differentiation, aging, and apoptosis, playing a crucial role in normal brain development and function [19].

3.2 The Impact of Glial Cell Lipid Metabolism Disorders on the Brain and Nervous System

Abnormal lipid metabolism in glial cells, especially in microglia, astrocytes, and oligodendrocytes, is associated with a series of brain development abnormalities and brain dysfunction. Lipid metabolism imbalance can directly affect cognitive function, emotional regulation, and motor coordination in the brain. Lipid droplets are spherical organelles commonly found in the cytoplasm, with a hydrophobic core composed of triglycerides and cholesterol. Lipid droplets are not only organelles for intracellular storage of neutral lipids but also participate in maintaining cellular energy metabolism homeostasis and lipid conversion. They are present in small amounts in the normal brain but accumulate more in the brain under aging or pathological conditions, especially in glial cells, while being less present in neurons [20]. In the central nervous system, lipid droplets are involved in the occurrence and development of neurodegenerative diseases by affecting the lipid composition and function of cells [21]. Microglia express Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), which participates in phagocytosis, calcium mobilization, energy metabolism, cytokine production, and immune response regulation [22]. It also participates in regulating cholesterol homeostasis and lipid uptake in myeloid cells. Microglia with dysfunctional TREM2 have reduced ability to phagocytize lipid-rich cell debris, leading to lipid accumulation and the formation of lipid-rich cells [23].

Astrocytes have high activity of lipid metabolism-related enzymes, and the lipids they produce are used by the brain to form synapses and maintain their normal function. The synthesis of cholesterol and fatty acids in astrocytes is regulated by Sterol-Regulatory Element Binding Proteins (SREBPs), and the reduction of SREBPs activity can damage the function of presynaptic terminals and synaptic

plasticity [20]. Fatty acids secreted by neurons combine with ApoE to form lipid droplets, which are then endocytosed and degraded by astrocytes through ApoE receptors, maintaining lipid balance in the brain and preventing the accumulation of fatty acids from being toxic to neurons. ApoE has three different subtypes: ApoE2, ApoE3, and ApoE4. Among them, ApoE4 is a high-risk factor for Alzheimer's disease (AD). The expression of the ApoE4 gene leads to an increase in lipid droplets formed in the endoplasmic reticulum of glial cells, thereby impairing the ability of glial cells to clear lipid droplets and increasing their sensitivity to lipid peroxidation, increasing the risk of AD. This indicates that ApoE4 drives lipid metabolism disorders in glial cells and increases the risk of disease induction [24]. Furthermore, ApoE4 impairs the ability of astrocytes to absorb lipid droplets from neurons. When astrocytes expressing ApoE4 were co-cultured with neurons that had impaired lipid droplet uptake and clearance, they failed to absorb the lipid droplets [25].

4. The role of glial lipid metabolism disorders in specific diseases

4.1 Alzheimer's disease

AD is one of the most common neurodegenerative diseases, with cognitive decline and memory decline as the main manifestations [26]. The typical pathological features of A D are the deposition of β-Amyloid (Aβ) to form amyloid plaques outside the cell, and the deposition of hyperphosphorylated microtubule-associated protein tau to form neurofibrillary tangles in the cell. In addition, AD is also accompanied by synaptic and neuronal loss, as well as reactive glial cell proliferation. Abnormal lipid metabolism, especially lipid metabolism related to fatty acid and phospholipid metabolism in the brain, is closely related to the occurrence and development of AD. The decreased level of glycerophospholipids may be associated with increased risk of neurofibrillary tangles and amyloidosis [27]. Other studies have shown that the level of glycerophospholipids in patients with AD is decreased, but the metabolites of glycerophospholipids are increased. These pro-inflammatory metabolites aggravate oxidative stress and inflammation by activating astrocytes and microglia, promoting the release of inflammatory factors and the formation of Aβ.

4.2 Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disease characterized by progressive loss of dopaminergic neurons in the substantia nigra. With the decrease of dopamine in the nigrostriatal system, patients often show typical motor symptoms, such as bradykinesia, increased muscle tone, resting tremor, postural instability and gait abnormalities. PD can be considered as a lipid-induced protein disease. Changes in lipid composition or metabolism can lead to changes in proteins, such as the aggregation of α-synuclein (α-Syn), which ultimately leads to neuronal death. Milena Fais et al believed that PD-related genes can affect cellular biological processes and lead to lipid changes. Some PD pathogenic or risk genes directly control the lipid metabolism of neuronal cells, and some PD pathogenic genes may indirectly control lipid metabolism, localization or signal transduction by controlling vesicle transport or lipid exchange between various organelles in cells. [28]. Similarly, Tae-In Kam et al. also considered many PD-related bases.

4.3 Cerebral Palsy

Cerebral palsy (CP) refers to a series of non-progressive dyskinesia syndromes caused by developmental brain damage. CP is the most common severe movement disorder in children, accompanied by a variety of complications including epilepsy, learning disabilities and communication difficulties, abnormal movement or posture. [30, 31]. The expression levels of CP-

related genes were different in different brain regions and different cell types. The three cell types with the highest expression were Purkinje cells, astrocytes and oligodendrocytes. Studies have shown that in mouse models, blocked lipid synthesis in oligodendrocytes can lead to severe demyelination and neurological symptoms, however, this damage will be greatly alleviated after a few months. The main source of lipids in the brain is astrocytes. Compared with the inability of oligodendrocytes to form myelin sheaths, the formation of myelin sheaths caused by impaired lipid synthesis in astrocytes is more severe and persistent [31]. The GPAM gene encodes a mitochondrial enzyme associated with lipid metabolism. There is a lot of evidence that there is a correlation between GPAM polymorphism and plasma cholesterol. GPAM deficiency can interfere with star by disrupting lipid metabolism.

4.4 Multiple sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by multiple inflammatory demyelination in the central nervous system, accompanied by neurological damage, axonal injury and reactive astrocyte proliferation [33]. In MS lesions, immune cells, including microglia and lipid-laden macrophages, destroy lipid-rich myelin. Compared with the myelin sheath of normal white matter with normal cell membrane lipid content and proportion, the decrease of myelin lipid content in the affected white matter of MS patients leads to an increase in the proportion of protein: lipid. A study has shown that with age, senescent phagocytes accumulate excessive myelin debris, which leads to the rupture of the lysosomal membrane and the formation of crystals of cholesterol, exacerbating the inflammatory response and hindering myelin regeneration. [34] Abnormal sphingomyelin metabolism is considered to be an important factor in the pathogenesis of MS. In the process of MS, the sphingosine-1-phosphate signaling pathway in astrocytes is activated, and the degree of demyelination and axonal injury is closely related to its activity level.

5. Conclusion Prospects

Glial cells play an irreplaceable role in maintaining the normal development of the brain and the normal operation of the nervous system. The premise of the normal physiological function of glial cells is the normal lipid content and proportion. Therefore, this article focuses on the physiological functions of glial cells and the relationship between lipid metabolism in glial cells and neurological diseases such as Alzheimer 's disease, Parkinson 's disease, multiple sclerosis, and cerebral palsy from three aspects: microglia, astrocytes, and oligodendrocytes. We can deeply understand the role of glial cell lipid metabolism in nervous system diseases. Future research needs to further reveal how abnormal lipid metabolism affects glial cell function, and explore intervention strategies for glial cell lipid metabolism, especially how to alleviate or treat diseases related to glial cell lipid metabolism disorders by intervening these metabolic processes, which may provide new breakthroughs in the treatment of neurological diseases. By studying the lipid metabolism of glial cells, we can better understand the role of these cells in neurodegenerative diseases and neurodevelopmental disorders. The in-depth understanding of glial cells and lipid metabolism is expected to provide an important theoretical basis for the development of new treatment methods and improve neurological diseases.

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