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Progress of Autophagy in Epilepsy Research

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Abstract

Epilepsy is a clinical syndrome caused by highly synchronized abnormal discharges of neurons in the brain. It is a common disease of the nervous system. The pathogenesis of epilepsy has not been fully understood yet. The main pathological changes after seizures are programmed neuronal death and glial proliferation. Autophagy is a catabolic process. Moderate autophagy is critical to maintain the homeostasis and cell health, while abnormal autophagy can lead to disease. A number of studies have proved that abnormal autophagy mechanism can lead to epilepsy, and there are also literatures that autophagy induced by endoplasmic reticulum stress can reduce the neuronal damage triggered by epilepsy, thus playing a protective role in neurons. This article reviews the relationship between autophagy and epilepsy in order to provide basis for further study of autophagy pathway and pathophysiology of epilepsy.

Keywords

Epilepsy, Autophagy, mTOR, Endoplasmic Reticulum Stress

1. Introduction

Epilepsy is a neurological disease characterized by long-term recurrence. It is due to the imbalance between excitatory and inhibitory neurotransmission in the central nervous system, resulting in abnormal discharge of neurons in the cerebral cortex. Epilepsy affects more than 50 million people worldwide [1]. At present, there are more than 9 million epileptic patients in China, and the number of new cases is up to 65 - 70 million every year, of which 30% are intractable epilepsy. The most significant steady-state changes in epileptic seizure activity include the accumulation of intracellular calcium and the increase of reactive oxygen species (ROS) production, and trigger neuronal death through a variety of mechanisms. Its basis is cell necrosis and apoptosis, and the damage to neurons depends on the entry of intracellular Ca^{2+} [2]. In addition, seizures can also

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lead to ion channel dysfunction, mossy fiber sprouting, glial hyperplasia, neurogenesis and inflammation [3] [4]. The pathogenesis of epilepsy is complex. Autophagy, as an important cell quality control method, also plays an important role in the occurrence and development of epilepsy. In mammals, autophagy is involved in many physiological processes, including the response to hunger, cell growth control, anti-aging mechanism and innate immunity. However, the disorder of autophagy plays a role in some diseases, such as cancer, cardiomyopathy, muscle diseases and neurodegenerative diseases. Autophagy can protect cells from further damage by removing certain toxins and pathogens, as well as denatured cytoplasmic components, such as condensed proteins or damaged organelles formed by misfolded or unfolded proteins; On the other hand, overactivated autophagy can lead to cell death, so autophagy is a double-edged sword for cells [5]. Autophagy changes exist in the mechanisms of many nervous system diseases, from neurodegenerative diseases to acute nerve injury, autophagy plays a corresponding role. The study of the correlation between autophagy and epilepsy is of great value for further elucidating the pathogenesis and prevention of epilepsy. Autophagy, as a biological research field that has attracted much attention in recent ten years, provides a new perspective for us to study the potential pathogenesis of epilepsy.

2. Molecular Mechanism and Biological Function of Autophagy

Autophagy, as its name implies, can be defined as "self digestion" of cells, which refers to the process in which organelles, proteins, protein complexes/oligomers, pathogens and other cellular components are transported to lysosomes for degradation and maintenance of cellular homeostasis [6]. According to different transmission mechanisms, autophagy can be divided into three types: macrophage, small autophagy and partner-mediated autophagy. These three activities are all related to nervous system diseases, because the transport mechanisms are different. There are also essential differences in the three processes of autophagy. [7]. Macrophage is an evolutionarily conservative lysosome mediated system for massive degradation of proteins, organelles and cellular components. It is characterized by inducing a small isolation membrane, which extends into a vacuole with a double membrane and can engulf a large number of cytoplasmic components, such as unfolded protein aggregates, damaged organelles, and invasive pathogens, such as bacteria [8]; Small autophagy means that lysosome membrane directly encapsulates substrate and degrades it in lysosome; Molecular chaperone mediated autophagy (CMA) is characterized by binding intracellular substrate proteins through molecular chaperones such as heat shock protein 70 (HSC70) and delivering them to lysosomes for digestion. This pathway is selective in protein clearance [9]. The main type of autophagy is macrophage (hereinafter referred to as autophagy).

Autophagy involves the following steps: first, autophagy begins with the formation of autophagosomes at the assembly site of the phage, and the formation

of autophagosome precursors is mediated by the activities of class III phosphatidylinositol 3 kinase (PI3K) and vacuolar protein classification 34 (Vps34). Subsequently, the bilayer membrane elongates and vesicles are formed through two ubiquitin-like reactions, collectively referred to as autophagosome elongation. The first ubiquitin-like reaction leads to the formation of the Atg12-Atg5-Atg16L1 complex, and the other leads to the formation of the LC3-II complex, which, notably, can interact with each other; then, the autophagosomes are transported in a kinetic protein-dependent manner to the lysosomes around the microtubule tissue center, where tethering, docking and fusion take place to achieve autophagosome maturation and fusion. Eventually, lysosomal hydrolases degrade cellular components captured in fused autophagy [10]. The close relationship between autophagy and the mechanism of apoptosis shows that autophagy not only plays a major role in cell survival, but also plays a vital role in type II programmed cell death. Autophagy is involved in both physiological and pathological processes [11]. Under physiological stress, autophagy mediates the clearance of misfolded, ubiquitinated proteins or damaged organelles, such as selective removal of mitochondria by autophagy to adapt to hunger [12], tumor inhibition [13], antigen presentation [14] and so on. In the pathological process, autophagy damage is also associated with a variety of human diseases, such as cancer [15], heart disease [16], autoimmune diseases [17] and nervous system diseases [18], including epilepsy [5]. In addition, autophagy is also considered as a target for the treatment of nervous system diseases.

3. Interaction between Autophagy and Epilepsy

3.1. Autophagy Mediates Epilepsy through mTOR Pathway

Mammalian rapamycin target protein (mTOR) is one of the key regulatory factors of autophagy. It is the main inhibitory signal to turn off autophagy under the condition of rich growth factors and nutrients, and plays a negative regulatory role in autophagy [19]. mTOR is actively involved in most key steps of neural development, such as the establishment of neuronal structure, the maintenance of synaptic strength, and the production of excitatory pyramidal neurons and inhibitory GABA neurons [20]. Abnormal activation of mTOR pathway can lead to a variety of epileptic syndromes, including hereditary epilepsy and various acquired epilepsy. Studies have shown that 24 hours after seizures and 5 weeks 3 days after status epilepticus (SE), epileptic activity can up-regulate mTOR signal pathway in biphasic state, and the persistent state lasts more than 30 minutes. The researchers used alginate, an ionic glutamate receptor agonist, to induce seizures in rats. Due to the wide distribution of glutamate receptors in the brain, the systemic application of alginate can stimulate many brain regions, especially hippocampal CA3 neurons. Alginate-induced discharges produce synchronous activity in a dense network of recurrent glutamate functional branching ligands, and this activity spreads to other marginal structures, including the dentate gyrus, CA1 and the entorhinal cortex. This synchronous activity activates many intracellular signal transduction pathways, including mTOR

signal transduction [21].

mTOR itself is strictly controlled by upstream regulatory factors, and the loss of function of these regulatory factors leads to abnormal over-activation of mTOR, which leads to epilepsy [22] [23]. mTOR-dependent translation control plays a key role in regulating the long-term morphological changes of neuronal spinous processes, dendrites and circuits. mTOR activation leads to the phosphorylation of multiple downstream effectors, such as eIF4E-binding proteins (4E-BPs) and S6 kinases, and stimulates the translation of mRNA subsets [24]. The role of the downstream mechanism of mTOR pathway in autophagy has also been shown to be related to the loss of function of TSC1 or PTEN [25]. Tuberous sclerosis (TSC) is a common autosomal genetic disease caused by mutations in tumor suppressor genes TSC1 and TSC2. It is characterized by lesions in multiple organs, including brain, skin, kidney, eyes and lungs [26]. Up to 80% - 90% of the TSC patients develop severe epilepsy, causing a significant decrease in the quality of life and a high morbidity [27]. TSC1 deficient mice and TSC2 deficient mice showed severe epileptic symptoms, accompanied by overactivation of mTOR and impaired autophagy. Hyperexcitability can be detected in the brains of patients with TSC and in neurons derived from induced pluripotent stem cells derived from patients with TSC [28]. It has been found that the decrease of inhibitory synaptic function can lead to overactivity of TSC1 deficient neurons [29]. On the other hand, PTEN deficiency can lead to severe epilepsy in mice with impaired autophagy [25]. PTEN and GATOR1 are both inhibitors of mTOR. PTEN is one of the tumor suppressor genes encoding plasma membrane lipid phosphatase, which can antagonize the upstream factor of PI3K-Akt signal of mTOR. GATOR1 activates GTPaseRagA/B, to inhibit activity under static and low amino acid conditions [30]. In view of the fact that many processes under the control of the mTOR pathway are likely to be accompanied by the loss of function of TSC1 or PTEN and other epileptogenic changes after the release of mTOR inhibition, the experimental data show that the impairment of autophagy may be one of several epileptogenic mechanisms downstream of mTOR [25].

Lafora disease (LD) is an autosomal recessive inherited disease characterized by seizures, progressive myoclonus, cognitive impairment, and basophilic inclusion bodies (Lafora bodies). LD is Progressive myoclonus is the most common form of epilepsy [31]. This disease is caused by mutations in the epilepsy-related protein laforin (encoded by the PME2A gene) or Malin (encoded by the PME2B gene). Laforin is a glycogen 6 phosphatase that can degrade glycogen chains. Malin is a ubiquitin E3 ligase. Mutations in the Laforin and Malin genes cause the abnormal accumulation of Lafora bodies in the cerebral cortex, substantia nigra, globus pallidus, and dentate nucleus. These inclusion bodies are formed by abnormal accumulation of glycogen. Knockout of the laforin gene, Malin gene, or both in mice will reproduce most of the symptoms of LD. Normal Laforin can inhibit the mTOR complex, allowing the autophagy mechanism to operate normally and maintain its function. On the contrary, when laforin is mutated, the autophagy pathway will be strongly inhibited by the excessive activa-

tion of mTOR, leading to glycogen clearance dysfunction. Mutations in the Malin gene lead to failure of autophagosome formation. Unlike Laforin-regulated autophagy, Malin-regulated autophagy does not depend on mTOR. Therefore, mutations of Laforin gene and Malin gene can lead to impaired autophagy and lead to accumulation of Lafora bodies in neurons [32].

Epilepsy caused by cortical malformations, such as focal cortical dysplasia type IIb (FCDIIb type) is a type of refractory epilepsy, its histopathology is similar to TSC, mainly manifested as abnormal neuron morphology, especially malformed neurons (DNs) and balloon cells (BCs). The BCs in the brains of FCD patients showed lysosome and autophagy-related proteins (including Beclin1, LC3, ATG5 and ATG12), as well as autophagy modulator DOR and autophagy receptor P62 Accumulation, which indicates that autophagy in FCD is impaired. This defect of autophagy can be reversed in vitro by inhibiting mTOR, which means that the abnormal activation of mTOR may directly lead to the defect of FCDIIb autophagy [33].

It can be seen that abnormal activation of mTOR is one of the main mechanisms of epilepsy. These findings may provide an important basis for further research on the role of mTOR in the treatment of epilepsy.

3.2. The Effect of Epilepsy on Autophagy

Pilocarpine is used to induce status epilepticus (SE), and it is found that SE may also cause autophagy dysfunction. The covalent binding of light chain 3 (LC3) I (apparent mobility, 18kd, mammalian homolog of yeast Atg8) and phosphatidylethanolamine forms LC3II (apparent mobility, 16kd), which is for autophagy It is an essential process called "LC3 drift" or "LC3 lipidation". Therefore, LC3 has two forms: LC3I is a cytoplasmic form, which is activated and modified into membrane-bound LC3II. The ratio of LC3II to LC3I was used to semi-quantify the amount of autophagosome formation. The detection of LC3 II by western blotting is a simple and quantitative method to determine the autophagy activity of mammalian cells. Studies have found that at 2, 8, 16, 24, and 72 hours after SE, the ratio of LC3II to LC3I increases significantly, and the relative abundance peak appears at 24 hours. These data indicate that autophagy in the hippocampus of rats is activated after SE [34]. Not only that, epilepsy is followed by oxidative stress, and oxidative stress is related to the induction of autophagy. In addition, ATP depletion, tumor necrosis factor alpha (TNF-α) and other induction factors increase and ion flux imbalance, these factors will lead Increased neuronal autophagy induction [35]. As a result, the excessive activation of autophagy may further aggravate epileptic seizures and form a vicious circle.

4. The Effect of Autophagy on Endoplasmic Reticulum Stress in Epilepsy

4.1. The Biological Functions of Endoplasmic Reticulum and Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) is the base for the synthesis of proteins, lipids

and carbohydrates. It is a vital organelle for the survival of neurons. It contains molecular chaperones and enzymes, which have calcium storage, signal transmission, and assist in protein folding and maturation [36]. Protein folding is a delicate process, and only correctly folded proteins will be modified in the Golgi apparatus and transferred to their destination [37]. On the other hand, misfolded or immature proteins will expose hydrophobic amino acid domains, thereby enhancing protein aggregation in the endoplasmic reticulum lumen, and are affected by the endoplasmic reticulum-related degradation (ERAD) mechanism or autophagy degradation pathway degradation [38].

The release of Ca^{2+} from the endoplasmic reticulum lumen to the cytoplasm can be the cause of endoplasmic reticulum stress (ERS). Various cellular stresses, especially endoplasmic reticulum calcium homeostasis and oxidative stress, may cause endoplasmic reticulum stress [39] [40]. Endoplasmic reticulum stress can be roughly divided into three types: unfolded protein response (UPR), endoplasmic reticulum overload response (EOR), and cholesterol regulation cascade (SREBP). The most important one is the unfolded protein response reaction (URP) [41], which requires inositolase 1 (IRE1), PKR-like endoplasmic reticulum kinase (PEKR), and active transcription factor 6 (ATF6) to complete the reaction process together [42]. The mammalian endoplasmic reticulum stress response includes four mechanisms: 1) inhibit protein synthesis to prevent further aggregation and accumulation of proteins; 2) transcriptionally induce ER chaperone genes to enhance folding ability; 3) transcriptionally induce ERAD genes to increase ERAD capacity/capacity; 4) Induce apoptosis to remove stressed cells [43].

4.2. Autophagy Regulation Can Reduce Endoplasmic Reticulum Stress

Epilepsy can cause endoplasmic reticulum stress by affecting the endoplasmic reticulum homeostasis, and then cause apoptosis through URP. The increase of intracellular Ca^{2+} has been shown to cause the initiation of autophagy, which can cause autophagy upregulation under endoplasmic reticulum stress. The increase in autophagic flux induced by endoplasmic reticulum stress also helps cells survive under adverse conditions [44]. Recent studies have shown that autophagy plays a key role in various neurodegenerative diseases, and FAM134B plays a functional role in autophagy [45]. Autophagy is an important process for maintaining cell homeostasis. Many studies have shown that autophagy modification can reduce the effects of seizures. Moderate endoplasmic reticulum stress can improve cell survival through UPR, which is mediated by endoplasmic reticulum transmembrane receptors (including IRE1, PERK and ATF6). Activation of these receptors will up-regulate the expression of ER partners (such as GRP78). On the other hand, the enhancement of endoplasmic reticulum stress will promote the activation of pro-apoptotic factors (such as CHOP) [46]. In the study, it was found that FAM134B over-expression inhibited GRP78 and CHOP expression and neuronal apoptosis, while FAM134B knockdown was the opposite.

This indicates that FAM134B alleviates neuronal endoplasmic reticulum stress and apoptosis. Autophagy can inhibit apoptosis by eliminating damaged organelles and misfolded and unfolded proteins, inhibiting caspase activation and clearing SQSTM1/p62, thereby protecting cells under endoplasmic reticulum stress. FAM134B is involved in promoting autophagy to relieve endoplasmic reticulum stress and prevent neuronal apoptosis, which means that FAM134B has a protective effect on endoplasmic reticulum stress and neuronal apoptosis caused by epileptic seizures, and this protective effect It is based on its regulation of autophagy [47].

5. Summary

Autophagy plays an important role in maintaining cell homeostasis and maintaining cell health. It is generally considered to be a major survival strategy for multicellular organisms. However, autophagy may also be caused by excessive self-digestion and degradation of main cell components. Autophagy can mediate epilepsy through the mTOR signaling pathway, however, epilepsy will in turn enhance autophagy, and excessively activated autophagy will aggravate epilepsy. On the other hand, studies have shown that the regulation of autophagy can reduce endoplasmic reticulum stress and nerve damage caused by epilepsy. It can be seen that the effects of autophagy on epilepsy are divided into advantages and disadvantages. Through in-depth research on the correlation between the two, it is of great value to further clarify the pathogenesis and prevention of epilepsy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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