The Role and Mechanism of Neuronal Autophagy in Alzheimer's Disease and Its Healthcare

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Abstract. Autophagy is the main pathway for the degradation of potentially toxic proteins and dysfunctional organelles. Studies have shown that autophagy dysfunction is closely related to a variety of neurodegenerative diseases. In Alzheimer's disease, autophagy is closely related to the generation and metabolism of β -amyloid protein and Tau protein and plays a special role in neuronal survival and apoptosis. Further research on the autophagy mechanism will contribute to the discovery of new therapeutic targets for AD. Royal jelly is an important bee product, which has long been used in the fields of traditional medicine, health food, and cosmetics. In recent years, based on its pharmacological activities such as anti-aging and promotion of nerve cell proliferation, royal jelly has been widely studied in the auxiliary prevention and treatment of Alzheimer's disease. This paper mainly discusses the mechanism of neuronal autophagy in Alzheimer's disease and introduce how can the royal jelly promote the development of new health products or drugs, so as to offer some references for the research and healthcare of Alzheimer's Disease.

Keywords: Alzheimer's disease · Autophagy · Autophagy lysosomal pathway · Beta-amyloid · Royal jelly

1 Introduction

Alzheimer's disease is a common chronic progressive degenerative disease of the central nervous system in the elderly. Its symptoms are characterized by slowly progressive memory and cognitive dysfunction. The pathological features were mainly senile plaques deposited outside the cell and neurofibrillary tangles accumulated inside the cell.

Autophagy is an intracellular pathway mediated by lysosomes to eliminate abnormal folding of potentially toxic proteins and dysfunctional organelles in tissues. It is an adaptive mechanism for cells to external environmental pressure and nutrient deficiency and is very important for stress induction, turnover of constituent proteins, and maintenance of normal cell homeostasis [1]. The lack of nutrients leads to the obvious activation of the autophagy pathway, and a large amount of protein degradation produces free amino acids, which can be metabolized in stress to provide the energy needed by the body.

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In recent years, autophagy has been found to be closely related to the pathogenesis of neurodegenerative diseases.

At the same time, the Royal jelly is considered a functional food because it contains a large number of biologically active substances, such as royal jelly main protein (MRJPs), royal pulp acid (10-HDA), phenolic compounds, and so on. They have pharmacological activities against cells and tissues in a variety of animal models, including neuromodulators activity, anti-aging activity, anti-inflammatory activity, and antioxidant activity [2] which have been used to treat a variety of diseases such as diabetes, cardiovascular disease, and cancer [3]. Previous reports show that royal jelly has obvious neuroprotective effects, can reduce cholesterol levels, improve Aβ pathological status, improve blood-brain barrier permeability and other properties, and can be used for the prevention and treatment of Alzheimer's disease [4].

Alzheimer's disease mainly occurs in the elderly population, and it is particularly important to delay aging and enhance physical health, so researchers believe that royal jelly has the potential for an adjuvant therapy.

2 Autophagy Process, Molecular Mechanism, and Signal Pathway

2.1 Autophagy Process

According to the different mechanisms and functions, autophagic lysosomal pathways can be divided into three types: giant autophagy pathway, small autophagy pathway, and molecular chaperone-mediated autophagy pathway.

The large autophagy pathway is characterized by the combination of double-membrane autophagosomes with lysosomes and the degradation of their contents [5]. Morphologically, the first step is nucleation, through which cells from isolated double-membrane structures called autophagy precursors. Autophagy precursors then elongate into a semicircle or crescent shape, wrapping abnormal organelles and proteins into autophagosomes. Finally, through the transport of the microtubule network, autophagosome and lysosome fuse to form autophagolysosomes, and the inclusions and intima are degraded. Large autophagy is the most common form of autophagy and is closely related to the pathogenesis of AD. The autophagic lysosomal pathway referred to in this paper only refers to the large autophagy pathway.

The small autophagy pathway refers to the process in which cytoplasmic components are directly enfolded into lysosomes through vacuolar transport chaperone complex and degraded by hydrolase without the formation of autophagosomes and autophagolysosomes [6].

About 30% of intracellular proteins with a specific sequence of KFERQ are degraded by the CMA pathway. The complex formed by HEAT shock protein 70 and its helper molecular chaperone can specifically recognize this sequence and transport the protein directly into the lysosome by lysosome-associated membrane protein 2A for folding and degradation.

2.2 Molecular Mechanisms and Signaling Pathways of Autophagy

The autophagy lysosomal pathway is mainly regulated by two signaling pathways: target of rapamycin (mTOR) and phosphoinositol-3 kinase (PI3-K).

The Class III phosphatidylinositol 3-kinase complex regulates the nucleation of autophagosome formation. It plays a regulatory role in the nucleation of autophagy precursor formation. Phosphatidylinositol can be phosphorylated by the PI3K enzyme complex to form phosphatidylinositol 3-phosphate (PI3P), which can attract Atg protein to the membrane of autophagosome and also play an important role in the membrane transfer process of the autophagosome [7]. As an autophagy inhibitor, 3-methyladenine can specifically inhibit the generation of PI3K complex and block the autophagolysosome pathway.

Mammalian target rapamycin is a highly evolutionarily conserved serine/threonine-protein kinase that participates in the regulation of multiple systems in cells, enabling cells to adapt to the external environment and nutritional changes. MTOR, as an upstream protein, inhibits autophagy by regulating the activity of downstream Atg. When activated, mTOR phosphorylates the Atg13, the regulatory subunit of Atg1 complex, preventing the complex formation and promoting autophagosome formation [8]. In addition, mTOR also regulates the activity of the ribosomal protein S6 (p70S6), which inhibits autophagy.

3 Role of Autophagy in AD

3.1 Effects of Autophagy on Aβ -Producing Secretase

SP is mainly formed by abnormal aggregation of β -amyloid protein hydrolyzed from the amyloid precursor protein. The plaques also include swollen and dystrophic dendrites and axons. Aβ is A 39–43 amino acid polypeptide structure of APP formed by cleavage of β- and γ- secretase. In cells where, basal autophagy levels are disrupted, gamma-secretase activity is enhanced by translational initiation factor 2 kinase α subunit [9]. Beclin1 protein expression was decreased in patients with severe AD. The deletion of Beclin1 heterozygosity in the transgenic mouse AD model leads to the interruption of autophagosome maturation, resulting in increased production and deposition of Aβ in mouse nerve cells, while reduced autophagy leads to reduced degradation of Aβ through APL [10]. Increased Aβ levels promote the formation of senile plaques.

3.2 Effect of Autophagy on Tau

Protein NFTs are mainly composed of Tau protein, a microtubule-associated protein, which is abnormally hyperphosphorylated and polymerized into a double helix form. The autophagolysosome system plays an important role in clearing Tau protein, and the dysfunction of the autophagolysosome system will lead to the formation of Tau oligomers and insoluble aggregates [11]. It has been found that rapamycin can improve pathological processes caused by hyperphosphorylation of Aβ and Tau proteins by increasing autophagy [12]. Treatment of cells with the autophagy inhibitor 3-methyladenine also caused tau to accumulate [13]. These studies all support the clearance effect of autophagy on Tau protein, and abnormal autophagy will lead to the formation of Tau oligomer.

3.3 Effects of Autophagy on Neuronal Survival and Apoptosis

Studies have shown that Aβ25–35 and Aβ42 can induce A strong autophagy response in SH-SY5Y cells. Laser confocal images of immunofluorescence dual staining showed that exogenous application of Aβ42 in serum can induce co-localization of Aβ42 and LC3 in neurons. These results suggest that autophagy may play A neuroprotective role by antagonizing Aβ -induced neurotoxicity [14]. Therefore, autophagy has a protective effect, but may also be a pathogenic factor, which is closely related to the pathophysiology of AD. Whether autophagy fights AD or causes AD may depend on different microenvironments and stages in the pathological process. Autophagy may play a protective role in the early stage of AD development, while it may cause cell degeneration and death in the late stage.

3.4 Therapeutic Significance of Autophagy in AD

Autophagy plays an important role in AD. Regulating autophagy to reduce the accumulation of toxic proteins such as Aβ can prevent or delay the occurrence and development of AD, providing A new strategy for the treatment of AD. Rapamycin inhibited the activity of the mTOR signaling pathway, increased autophagy, reduced the formation of the Aβ pathologic pathway and NFTs, slowed or prevented the progression of AD in transgenic mice, and alleviated cognitive deficits. Studies have shown that only in the early stages of AD, rapamycin-induced autophagy is of therapeutic significance [15]. Ca^{2+} ion channel antagonist isradipine can improve autophagy function by inhibiting the influx of calcium ions from nerve cells in the hippocampus, weaken Aβ oligomer toxicity and reduce Tau protein levels by inhibiting Ca^{2+} influx in hippocampal neurons [16].

4 Treatment and Healthcare of Alzheimer's Disease

General nursing, try not to change the living environment, when you have to change the environment, pay attention to try to be similar to the previous living environment, you can carry the bedding that the elderly have been using, like daily necessities; clothes are stacked in the order of wearing, avoiding too many buttons, choosing shoes without ties, eating regularly, assisting the elderly to wash their hands before eating, explaining the steps of eating, feeding if necessary; choose foods rich in trace elements such as lecithin, vitamin A, vitamin E, zinc, selenium, etc., and limit the intake of aluminum-containing foods, such as fritters. In clinical nursing work, paper-cutting activities and painting activities are carried out regularly to train patients' ability to perform, so that patients can exercise the flexibility and coordination of limbs in activities. In symptomatic care, for patients with memory impairment, the elderly should be encouraged to recall past life experiences, their families should help them recognize the people or things in their current lives; often use sensitive and pleasant words of the elderly to communicate with them, gain the trust of the elderly, and improve the memory status; in this way, it can set up regular work and rest time for the elderly so that it can establish a regular life; for some daily behaviors that the elderly often forget, a striking sign can be set up to help

them remember. For patients with sleep disorders, an environment conducive to sleep rest should be arranged to help patients comply with previous sleep habits and methods, increase daytime activity, and reduce daytime sleep time; reduce the amount of activity before bedtime; drink a cup of hot milk before going to bed, avoid coffee or strong tea, soak your feet in hot water before going to bed, take a bath, or listen to some soothing music; avoid drinking plenty of water before going to bed; when sleep disorders are severe, sleep interventions (sleep behavior interventions and sleep restriction therapy) or traditional acupuncture care and Herbal foot baths may be used to help patients sleep. When the patient has a behavioral disorder, find out the cause when the patient refuses to bathe, find out the way to cope with different reasons, and the patient who refuses to eat, re-customize the time and posture of eating, and if necessary, give nasogastric treatment to ensure nutritional needs. In order to prevent the patient from getting lost, the patient's name, address, telephone, and other information can be written on the card and placed on the patient. The toilet should be clearly marked the location for patients with urinary incontinence; the elderly should be guided to the toilet as soon as possible when they have a desire to defecate. Family members or medical staff should communicate more with patients to meet their psychological needs, and give anti-anxiety drugs when patients have symptoms such as anxiety. As the patient's ability declines, irritability will occur, and the patient should be comforted and persuaded, pay attention to the tone and words when persuading the patient, avoid irritating words, talk to the patient about something else, and use the method of transfer to keep the patient's mood stable.

5 Conclusion

It is estimated that more than 50 million people with Alzheimer's disease will be affected worldwide in 2020, and this number is expected to exceed 150 million in 2050. Currently, the economic burden of the disease is about $1 trillion a year, and by 2030, that cost will double. Obviously, Alzheimer's disease has become one of the important public health challenges facing human society today. Over the past few decades, a variety of drugs have been used to treat Alzheimer's disease for a long time, but the effects are not ideal and side effects are obvious, such as angioedema, microbleeds, and neuronal hyperactivity. Therefore, the scientific community has also begun to focus on the prevention of Alzheimer's disease, developing corresponding drugs or functional foods. Royal jelly is gradually recognized as a natural functional food with its potential role in preventing or treating Alzheimer's disease. This paper reviews the mechanism of action of royal jelly in the prevention and treatment of Alzheimer's disease by summarizing the roles of royal jelly antagonistic Aβ production and aggregation, reducing cholesterol levels, alleviating oxidative stress, enhancing neuronal function, and regulating the binding level of insulin to receptors. In order to further study the mechanism of action of royal jelly and its active ingredients on Alzheimer's disease, it will provide experimental design ideas and facilitate the development of new royal jelly health products or drugs in the future.

Although Alzheimer's disease brings a heavy burden to patients and families, but the correct care for improving the quality of life of patients, promoting the recovery of disease has important significance, with the rise of the proportion of social aging, the incidence of Alzheimer's disease is also increasing, is bound to increase the social burden, hope

that society and individuals in the elderly and health in advance intervention, for the coming aging to do a good job of planning and guidance.

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