Research progress on pathogenesis and prevention strategies of Alzheimer's disease

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Abstract. Alzheimer's disease (AD), a degenerative disease of the nervous system, typically develops episodic memory impairments in affected individuals, followed by other cognitive symptoms, including language, executive, and vision Spatial function is difficult and eventually leads to dementia. The etiology of Alzheimer's disease is not yet clear, and the pathogenesis is very complex. This review systematically summarizes the pathogenesis of AD by reviewing the research in related fields, and discusses the prevention and treatment of AD. The future direction is expected to provide new ideas for the prevention and treatment of the disease.

Keywords: Alzheimer's disease, Neurodegenerative diseases, Cognitive impairment

1. Preface

With the acceleration of the global aging process, the improvement of living standards and medical technology, and the prolongation of human life expectancy, the prevalence of neurodegenerative diseases continues to rise. Currently, 50 million people worldwide have dementia, and by 2050 this number is expected to increase to 130 million. As a neurodegenerative disease that is difficult to prevent and cure, AD brings serious economic and living burdens to the elderly and their families. But so far, the scientific community has different opinions on the pathogenesis of AD, and the lack of effective prevention strategies and treatment methods has also become a great challenge. Therefore, based on the current mainstream AD pathogenesis, this paper deeply discusses the future direction of AD prevention and treatment, and points out the direction for AD prevention and treatment.

2. Mainstream AD pathogenesis mechanism

The pathogenesis of AD is complex, mainly due to abnormal β-amyloid (Aβ) metabolism, hyperphosphorylation of tau protein, etc., and is also controlled and affected by other factors [1].

2.1. Amyloid Cascade Theory

Since the overproduction of Aβ is involved in genetic mutations, scientists have studied Aβ earlier and deeper in AD. Amyloid β (Aβ) begins to aggregate and accumulate in cortical extracellular plaques about 10-30 years before the onset of dementia. in the block.

Aβ is formed by the hydrolysis of amyloid precursor protein (APP) by β-secretase and γ-secretase in the brain, and there are three main types: Aβ1-40, Aβ1-42 and Aβ1-43. Among them, Aβ42/43 is a β-layered structure with strong hydrophobicity, easy deposition, and high neurotoxicity, which is the main factor leading to AD neurodegeneration and cognitive dysfunction [2]. TAN et al. [3] proposed that Aβ oligomers can interfere with neuronal cell membrane function and trigger neuronal K+ efflux, resulting in the induction of NLRP1 formation by low intracellular K+ concentrations. The NLRP1 inflammasome recruits downstream caspase-1 effectors, promotes the maturation of IL-18 and IL-1β precursors, and releases them outside the cell to trigger an inflammatory response and induce neuronal death. In addition, HAN et al[4] used Aβ1-42 to stimulate mouse cortical neurons, and found that Aβ1-42 could directly induce the death of mouse cortical neurons through the pyroptotic pathway. RP3, caspase-1 and GSDMD protein expression increased. siRNA silencing of caspase-1 and GSDMD can significantly inhibit Aβ1-42-induced neuronal cell death, further demonstrating that Aβ1-42 induces neuronal pyroptosis through the caspase-1/GSDMD signaling

pathway [5]. Necrosulfonamide (NSA), a GSDMD-NT oligomerization inhibitor, was used to pretreat mouse cortical neurons with NSA. The results showed that NSA pretreatment could inhibit Aβ1~42-induced pyroptosis, mainly by inhibiting Cell membrane permeability and inflammatory factor release, indicating that inhibition of GSDMD-NT oligomerization can significantly reduce neuronal pyroptosis. Therefore, at the cellular level, it is proved that the caspase-1/GSDMD pathway is the main mechanism of Aβ1-42-induced neuronal pyroptosis. [6].

However, whether Aβ deposition is the initial stage of AD remains controversial. Some studies have found that amyloid plaques appear earlier than neurofibrillary tangles and neuronal loss, but other studies have found pathological changes in AD to appear first in the entorhinal area, where neurofibrils appear in the absence of Aβ deposition tangles [7].

One of the hallmarks of Alzheimer's disease (AD) has long been the buildup of amyloid beta plaques in the brain, and scientists have been focusing on treatments to remove the plaques, but recent findings have upended this. cognition. In fact, amyloid plaques are the result of AD, not the cause. Alzheimer's symptoms appear to depend on the depletion of normal soluble Aβ42 protein, which is in a soluble state rather than aggregated into plaques, so it is possible that future treatments most relevant to the Alzheimer's program are These brain soluble Aβ42 proteins were supplemented to normal levels [8].

2.2. The theory of abnormal phosphorylation of Tau protein

Numerous studies have shown that abnormal tau protein plays a key role in the development of neurodegeneration and memory impairment in Alzheimer's disease. Because the accumulation of hyperphosphorylated tau protein in cells leads to endoplasmic reticulum stress, mitochondria lengthen and accumulate around the nucleus, dysfunction; phosphorylated tau protein aggregation can also lead to microtubule depolymerization and damage to axonal transport function. Reduced spine formation and impaired synaptic transmission; hyperphosphorylated tau protein aggregation can also lead to autophagy disorders, forming a causal alternation and vicious cycle, aggravating the aggregation of phosphorylated tau protein, and ultimately leading to learning and memory impairment.

In recent years, drug research on Tau protein has also become a hot spot, such as vaccines against Tau protein, antisense RNA, modulators of various modification-related enzymes, etc. Since Tau protein mainly aggregates in cells, effectively penetrating the cell membrane may be one of the obstacles that macromolecular vaccines must overcome; since Tau aggregation in Alzheimer's disease is mainly caused by post-translational modification, it may be difficult to inhibit its synthesis to achieve good results; Since an enzyme that only acts specifically on tau protein and does not act on other substrates has not been found so far, strategies to modulate enzyme activity may lead to more toxic side effects than therapeutic effects.

3. The role of genetic factors

Studies have shown that mutations in PS1, PS2 genes (genes encoding presenilin) and APP genes (genes encoding apolipoprotein ApoE4) can lead to excessive Aβ42/43 production in the brain. ApoE protein is an important apolipoprotein component in plasma lipoprotein. It is hydrolyzed by β-secretase and γ-secretase successively to produce Aβ. Presenilin is the active center of γ-secretase complex. APP, PS1, PS2 gene mutations can selectively cause Excessive Aβ42/43 is produced in brain tissue; at the same time, ApoE4 can inhibit the clearance of Aβ by astrocytes and neurons [5-6].

Therefore, genetic factors contribute to the pathogenesis of AD by affecting the production or clearance of Aβ, and the exploration of AD susceptibility genes may be a major breakthrough.

4. Research progress of other influencing factors

In recent years, scientists have discovered that neuroinflammation, sleep, and the periphery all play a role in the formation and progression of AD to varying degrees.

4.1. Influence of neuroinflammation

Neuroinflammation is one of the main causes of nerve cell necrosis. Neuroinflammation is mainly mediated by microglia. The P2X7 receptor is an ATP-gated ion channel receptor, which is mainly present in immune cells and is mainly expressed on the surface of microglia in brain tissue. The expression of P2X7 was increased in the brain tissue of AD mice, and it was mostly located in the microglia around the senile plaques, indicating that Aβ may activate the NLRP3 inflammasome through the P2X7 receptor expressed on the surface of microglia, and induce a dependent caspase-1/ Pyroptosis in GSDMD [9].

Microglia play a dual role in the development of AD: under normal circumstances, microglia can reduce the appearance of cognitive impairment during AD formation by removing excess amyloid in the brain; however, if microglia are overactivated, It increases the release of pro-inflammatory factors (such as TNF-α) and promotes the formation of AD [10].

DNLRP3 is the main pattern recognition receptor involved in the process of pyroptosis, and it is also the most widely studied inflammasome ASC. As the adaptor protein of the NLRP3 inflammasome, it also plays an important role in pyroptosis. In vitro studies have found that compared with the control group, the expression of ASC in AD cell model is increased, and the ASC-Aβ complex can inhibit the clearance of Aβ by primary microglia. The possible mechanism is that in the presence of ASC, the activity of NLRP3 inflammasome is enhanced. , triggering the inflammatory cascade and inhibiting the phagocytic activity of microglia [11]. ASCs have also been shown to interact with pathogenic Aβ1-42 extracellularly, enhancing their toxic effects, with enhanced ASC, caspase-1 activity, and increased pro-inflammatory cytokines in microglia exposed to ASC-Aβ complexes . Inflammasomes may also be involved in Aβ production. Acute-phase proteins after bacterial infection promote the formation and activation of inflammasomes under the stimulation of cytokines, and are also associated with non-specific killing mechanisms, which may initiate the process of Aβ homeostasis via caspase cascade in AD, resulting in increased Aβ production [12] .

Therefore, the inflammatory release pathway of microglia can be used as the target of drug research, and the development of drugs that can selectively release inflammatory factors will be helpful for the treatment of AD.

4.2. The cleansing effect of sleep on Aβ

Scientists have discovered that there is a "drainage" network called the glymphoid system in the mouse brain, which is made up of glial cells. These glial cells are located around neurons that generate electrical impulses. The glymphatic system uses cerebrospinal fluid to collect and break down harmful metabolic waste produced by the work of neurons. During deep NREM sleep, glial cells in the brain shrink in size, creating more space for cerebrospinal fluid to clear metabolic waste, including Aβ. Similarly, Aβ levels in the cerebrospinal fluid of subjects were significantly increased due to the lack of cleansing after deep NREM sleep in human trials [13].

Therefore, maintaining adequate sleep helps to clear Aβ in the body, which is of great significance for the prevention of AD. Suvorexant is an orexin receptor antagonist approved by the US FDA, which may be effective in the treatment of insomnia, and may create the possibility for further research on the relationship between orexin and AD. A direct positive impact on quality of life [14].

4.3. Peripheral effects

Studies have shown that in mice, Aβ produced by the liver can enter the brain through the blood through triglyceride-rich lipoproteins. The accumulation of Aβ in the brain caused neurodegeneration and brain atrophy in the experimental mice, along with neurovascular inflammation and brain

capillary dysfunction, common hallmarks of Alzheimer's disease. This suggests that peripherally derived Aβ has the ability to cause neurodegeneration and suggests that Aβ produced in the liver is a potential contributor to human disease [15].

Therefore, lifestyle factors may play a more important role in the prevention of AD, including high-fat diet, which may accelerate the production of Aβ in the liver, and further research is still needed, perhaps through the individual's diet and some specific targets for lipoprotein amyloid. Protein-based drugs to resolve the massive deposition of Aβ in the blood, thereby reducing the risk of Alzheimer's disease or slowing the progression of Alzheimer's disease [15].

5. Summary and Outlook

Lifestyle factors play an important role in the prevention of AD. As an individual, you should maintain a good diet and work and rest habits. If necessary, take some drugs that promote sleep and regulate circadian rhythm to help Aβ be excreted from the brain, and use some special-targeted lipoproteins. Amyloid drugs to address the massive deposition of Aβ in the blood. In addition, new AD biomarkers and detection methods are also used in the prevention process, early detection, early treatment, and early recovery.

On the therapeutic side, the amyloid-beta cascade hypothesis is currently challenged, with a growing body of research finding that future treatments most relevant to the Alzheimer's program may be supplementing these brain-soluble Aβ42 proteins into normal level. Targeted drugs for Tau have become a new direction, and the exploration of AD susceptibility genes is still a big breakthrough. The inflammatory release pathway of microglia can be used as a target for drug research. The development of drugs that can selectively release inflammatory factors will Contributing to the treatment of AD, the cleansing effect of sleep on Aβ is worth thinking about, and the effect of peripheral production of Aβ on the brain may produce a new subversion in the field of prevention and treatment.

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