Amyloid-β and Neurodegeneration: Pathological Mechanisms and Therapeutic Challenges in Alzheimer's Disease

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Abstract. Alzheimer's Disease (AD) is a common neurodegenerative disease and one of the leading causes of dementia. The prevalence of AD continues to rise globally, with the number of sufferers expected to exceed 139 million by 2050. The core pathological features of AD include beta-amyloid (Aβ) deposition, abnormal phosphorylation of Tau protein, synaptic dysfunction, and neuroinflammation. Among them, the abnormal metabolism of Aβ is considered to be the key pathogenic factor of AD, and the amyloid plaques formed by its accumulation can disrupt neuronal signaling, induce neuroinflammation, and accelerate neurodegeneration. In addition, the interaction of Aβ with Tau protein intensifies the formation of neurofibrillary tangles (NFTs), further impairs nerve function. In terms of early diagnosis, advances have been made in the study of Aβ-related biomarkers, including positron emission tomography (PET) imaging, cerebrospinal fluid and blood testing, and multi-omics analysis techniques, which provide new tools for early detection and accurate diagnosis of AD. At the same time, there is growing interest in strategies to prevent AD, such as a healthy diet, regular exercise, cognitive training, and chronic disease management, which may help reduce the risk of developing the disease. This article reviews the mechanism of Aβ in AD, and discusses the treatment and prevention strategies based on Aβ, in order to provide new ideas for the early diagnosis, precise treatment and multi-target intervention of AD.

Keywords: Amyloid-β, Neurodegeneration, Alzheimer's Disease.

1. Introduction

Alzheimer's Disease (AD) is a common neurodegenerative disease (NDD), which is one of the main causes of AD. Globally, the prevalence of AD continues to rise. According to the World Health Organization (WHO), as of 2023, there are approximately 55 million dementia patients worldwide, of whom AD accounts for 60%-70%. The number of AD patients worldwide is expected to exceed 139 million by 2050 [1]. The disease is characterized by a progressive decline in cognitive function, including memory loss, cognitive impairment, and behavioral abnormalities, which ultimately lead to the inability of patients to take care of themselves and place a heavy burden on families and society.

The pathological mechanism of AD is relatively complex, and the theories that have been well studied include β-amyloid (Aβ) deposition, abnormal phosphorylation of Tau protein, neuroinflammatory response, and synaptic dysfunction, etc. Among them, the abnormal metabolism of Aβ protein is considered to be the key pathogenic factor of AD. Aβ is produced by the hydrolysis of amyloid precursor protein (APP) by β- and γ-secreting enzymes. The main subtypes of Aβ include Aβ40 and Aβ42, which are more likely to aggregate to form amyloid plaques. It is highly toxic to neurons [2]. Aβ plaque deposition not only disrupts interneuronal signaling but also induces abnormal phosphorylation of Tau protein to form neurofibrillary tangles (NFTs), which further intensifies neuronal damage [3]. In addition, Aβ also activates microglia and astrocytes, triggering chronic inflammatory responses and accelerating the progression of the disease.

In recent years, there has been some progress in the treatment of Aβ, in which monoclonal antibody therapies (such as Aducanumab, Lecanemab) have been approved by the FDA for the treatment of AD and have shown some Aβ clearance effect. In addition, small molecule inhibitors such as BACE inhibitors and gamma-secretase modulators are also being explored in clinical trials. However, the clinical effectiveness of these therapies is still controversial, such as significant individual differences in patients, high treatment costs, and some drugs are associated with side effects such as brain edema. Thus, although the Aβ hypothesis has dominated AD research, the limitations of single-target therapy

have prompted investigators to explore multi-target intervention strategies, such as combination Tau inhibitors, anti-inflammatory therapy, and gene editing techniques such as CRISPR-Cas9.

In this context, this paper focuses on the mechanism of action of Aβ in AD and discusses the research progress of its related treatment strategies. By reviewing the experimental and clinical trial data in recent years, we hope to further clarify the Aβ-related pathological mechanism and provide A new perspective for the early diagnosis, precision treatment and multi-target intervention strategies for AD.

2. Pathophysiology of Aβ in Alzheimer's Disease

2.1. A-β

A-β is A peptide produced by the amyloid precursor protein (APP) through the continuous cleavage of β-secretase (BACE1) and γ-secretase. The most pathogenic A-β42 is extremely prone to aggregating and forming amyloid plaques, which are one of the main features of AD pathology. These plaques disrupt communication between neurons, trigger inflammatory responses, and promote neuronal death, leading to gradual cognitive decline in AD patients.

The accumulation of A-β is thought to be the result of an imbalance between its production and clearance. Under normal circumstances, A-β is effectively cleared through A variety of pathways. In AD, however, this balance is upset, leading to excessive deposition of A-beta and triggering neurotoxicity. The toxic effects of A-β involve multiple mechanisms, including direct damage to neurons, induction of oxidative stress, and disruption of cellular homeostasis.

2.2. Mechanism

The idea that Aβ oligomers are the main toxin responsible for synaptic dysfunction and cognitive impairment in AD patients has attracted widespread attention and contributes to our understanding of the mechanism of the disease [4].

2.2.1 Synaptic Dysfunction

Aβ oligomers can interfere with synaptic signaling, resulting in impaired memory and learning. Studies have shown that these oligomers inhibit long-term potentiation (LTP), a process closely associated with synaptic plasticity and memory formation. In experiments, the presence of Aβ oligomers inhibited LTP for A few minutes without affecting baseline excitability, suggesting that the primary mechanism of action is impaired signaling rather than physical degradation of synapses [WZ1] [5]. After prolonged exposure to Aβ oligomers, neurons eventually undergo selective death, A process associated with NMDA receptor signaling that can be prevented by knocking out the Fyn tyrosine kinase. These findings have led to the "oligomer hypothesis", which suggests that Aβ oligomers are A major contributor to memory loss and disruption of synaptic plasticity in AD, and that they play a role in the early stages of the disease.

2.2.2 Pathological changes of Tau

A-β promotes hyperphosphorylation of tau protein, leading to the formation of neurofibrillary tangles (NFTs), another major pathological feature of AD. The exact association between A-β and tau pathologic changes is not fully understood, but studies suggest that A-β may induce tau protein phosphorylation by activating kinases, thereby disrupting microtubule stability [6]. This process causes tau proteins to misfold and aggregate, further impinging neuronal function and accelerating neurodegeneration.

2.3. Metabolism

The metabolic process of A-β involves fine regulation of its production and clearance mechanisms.

2.3.1 Generation Path

A-β is produced in two main ways: The way amyloid precursor protein (APP) is processed plays a key role in the pathogenesis of AD. APP is metabolized mainly through two pathways: the amyloid pathway and the non-amyloid pathway. In the amyloidosis pathway, APP is continuously cleaved by β-secretase and γ-secretase to produce Aβ peptide, of which Aβ40 and Aβ42 are the most dominant products. These Aβ peptides tend to aggregate and form amyloid plaques, which are considered to be important markers of pathological changes in AD. In contrast, the non-amyloid pathway is primarily mediated by alpha-secretory enzymes that avoid Aβ production and produce soluble APP alpha (sAPP alpha), which has neuroprotective effects and helps maintain synaptic function and cell survival [7]. Gamma-secretase plays an important role in APP processing. It is composed of multiple proteins and has a complex regulatory mechanism. Recent studies have revealed the three-dimensional structure of gamma-secretase, providing an important basis for understanding its function [7]. Structures resolved by single-particle cryo-electron microscopy showed that the gamma-secretase consists of a horseshoe-shaped transmembrane domain containing 19 transmembrane helices and has a large extracellular domain from the nicastrin subunit located above the cavity formed by the transmembrane structure aps201728. This structural information helped researchers better understand how gamma-secreting enzymes process APP and affect Aβ production. Specifically, it helps to identify the active site of presenilin (the catalytic core of gamma-secretase) and the mechanism of substrate recognition. In addition, the spatial arrangement of the various components of gamma-secretase also provides important guidance for the development of gamma-secretase inhibitors and regulators, which are expected to reduce Aβ production and provide potential therapeutic strategies for slowing the progression of AD.

In summary, the processing pathway of APP directly determines the generation and clearance of Aβ, and therefore becomes an important focus of AD research. The amyloid pathway leads to Aβ production through A cascade of β-secretase and γ-secretase, while the non-amyloid pathway inhibits Aβ formation and promotes neuroprotection through α-secretase action.

2.3.2 Clearing Mechanism

The removal of Aβ from the brain plays a crucial role in preventing its accumulation and the formation of amyloid plaques, which are closely linked to AD. Several enzymes, including neprilysin (NEP) and insulin-degrading enzyme (IDE), are involved in breaking down Aβ and regulating its levels. Studies have shown that a reduction in these enzymes' activity can lead to increased Aβ buildup, contributing to disease progression.

NEP is widely distributed in the body, including the brain, and is responsible for degrading various peptides, including Aβ. Research suggests that NEP levels are lower in brain regions most affected by amyloid plaques in AD patients [8]. Similarly, IDE plays a role in both insulin metabolism and Aβ degradation, and its dysfunction has been associated with an increased risk of AD. Other proteases, such as plasmin and endothelin-converting enzyme (ECE-1), have also been found to contribute to Aβ clearance.

Given the role of these enzymes in Aβ breakdown, enhancing their activity has been considered a potential therapeutic strategy for AD. However, since they also regulate other important biological processes, increasing their function could have unintended effects. Further research is needed to better understand how to safely target these clearance mechanisms to reduce Aβ accumulation without disrupting normal physiological function.

2.3.3 Genetic factors

Multiple genetic factors influence Aβ metabolism and are strongly associated with the risk of developing AD. Mutations in key genes may alter the processes of Aβ production, aggregation, and clearance, thereby affecting the disease process. APP mutations alter the pattern of Aβ production and aggregation. Among them, some mutations lead to increased production of Aβ42, and Aβ42 has A stronger tendency to aggregate and easily form amyloid plaques, thus accelerating the pathological progression of AD [9]. In addition, mutations in PSEN1 and PSEN2 affect the activity of gamma-

secretase, resulting in A change in the proportion of Aβ production, especially an increase in the proportion of Aβ42/Aβ40, which further promotes the deposition and toxicity of Aβ. Another important genetic risk factor is the APOE4 allele. APOE4 not only enhances Aβ aggregation, but also reduces its clearance efficiency, making it easier for Aβ to accumulate in the brain. Studies have shown that individuals with APOE4 are more likely to develop AD than those with APOE3 or APOE2, and have an earlier age of onset with a significantly increased risk.

3. Application status based on Aβ

3.1. Early symptoms and biomarker development

Early detection of AD is essential for timely intervention, and advances in biomarker research have significantly improved the accuracy of diagnosis. Imaging techniques have played an important role in the diagnosis of AD, such as positron emission tomography (PET) combined with Aβ tracers (such as Pittsburgh Compound B, PiB), which can visualize amyloid plaque deposition in vivo, providing an important basis for early identification of the disease. In addition, body fluid biomarker detection also provides biochemical evidence for the pathological characteristics of AD. Cerebrospinal fluid (CSF) and blood samples can be used to measure Aβ42, Aβ40 and tau protein levels, which are closely related to the pathogenesis of AD. In addition to imaging and body fluid detection, omics analysis techniques (including genomics, proteomics, and metabolomics) are also widely used in AD studies [10]. These methods are able to identify early molecular changes in the disease process, contributing to the discovery of new biomarkers to further refine the early diagnosis system for AD and provide potential targets for individualized therapy.

3.2. Treatment strategy

The treatment of AD is still focused on relieving symptoms, and existing drugs are difficult to stop the progression of the disease. As a result, researchers are exploring more effective treatments to delay disease progression or improve neurological function.

FDA-approved drugs mainly include cholinesterase inhibitors (such as Donepezil, Rivanstigmine, galantamine) and the NMDA receptor antagonist Memantine. These drugs improve cognitive function by modulating neurotransmitter levels, but are unable to fundamentally alter the course of the disease. In addition, some combination drugs (such as Namzaric) combine different mechanisms of action in order to improve the therapeutic effect. On this basis, novel therapeutic strategies are mainly focused on reducing Aβ accumulation and nerve damage. Among them, small molecule inhibitors are being studied to prevent Aβ aggregation, and immunotherapy aims to use antibodies to clear Aβ, thereby reducing the formation of amyloid plaques. At the same time, secretase inhibitors reduce the production of Aβ by regulating the activity of enzymes associated with its production, but since these enzymes also play an important role in physiological processes, their long-term inhibition may bring side effects, so further optimization is still needed. In addition to Aβ-related treatments, therapies targeting tau protein are also receiving attention. Abnormal phosphorylation and aggregation of tau protein is considered to be an important factor leading to neuronal damage. Therefore, researchers are exploring therapeutic methods to inhibit tau aggregation, stabilize microtubules, and promote tau degradation. In addition, anti-inflammatory therapy is also one of the potential directions, because neuroinflammation plays an important role in the pathological process of AD, and regulating the immune response may help reduce nerve damage.

Gene regulation and neuroprotection are also the focus of future treatments. microRNA (miRNA) plays A role in the production of Aβ and the regulation of tau protein, and intervening in its expression may become a new therapeutic strategy [7]. In addition, some natural compounds and neuroprotectants have been found to have anti-Aβ aggregation, anti-oxidation and promotion of neuronal survival, providing A new direction for AD research. Although these novel treatments are still in the research stage, with a deeper understanding of the pathogenesis of AD, it is possible to

combine multiple treatment strategies in the future to improve the effectiveness of early intervention and provide patients with more effective treatment options.

4. Prevention

Prevention of AD focuses on lifestyle adjustments and risk management to reduce the risk of developing the disease or delay disease progression. Research suggests that factors such as a healthy diet, regular exercise, cognitive training, and chronic disease management may play a role in preventing AD.

Dietary interventions are considered important for improving brain health, such as the Mediterranean diet and DASH diet, which are rich in antioxidants and healthy fats that help reduce neuroinflammation and oxidative damage [11]. Physical activity is also key to preventing AD, as regular exercise improves blood circulation, reduces inflammation, and helps clear Aβ from the brain, thereby improving cognitive function.

Cognitive training helps strengthen neural connections by keeping the brain active. For example, mental activities such as learning new skills, reading and solving puzzles are thought to increase the brain's cognitive reserve, thereby reducing the risk of cognitive decline. In addition, chronic disease management is also an important part of preventing AD. Controlling conditions such as high blood pressure, diabetes, and high cholesterol can reduce the risk of disease by reducing damage to blood vessels and the nervous system in the brain.

Overall, the prevention of AD needs to consider a variety of factors, and a healthy lifestyle may reduce the possibility of disease occurrence to some extent. In the future, further research may help develop more precise prevention strategies and improve the effectiveness of individualized interventions.

5. Conclusion

AD is A complex NDD, its core pathological mechanism involves Aβ deposition, Tau protein abnormality, synaptic dysfunction and neuroinflammation. Abnormal metabolism of Aβ is believed to be the main causative factor of AD, and the imbalance between its production and clearance leads to the accumulation of toxic Aβ42, which in turn triggers neurological damage and cognitive decline. Although single-target therapies against Aβ have made some progress, such as the development of monoclonal antibodies and small molecule inhibitors, their clinical efficacy is still limited, prompting investigators to explore multi-target intervention strategies, such as combined Tau inhibitors, anti-inflammatory therapy, and gene editing techniques.

In addition, the means for early detection and diagnosis of AD continue to evolve, and PET imaging, biomarker analysis and multi-omics techniques provide new directions for accurate diagnosis. In terms of prevention, a healthy lifestyle, such as proper diet, exercise and cognitive training, is thought to reduce the risk of AD. However, many challenges remain in the current study, including individual differences in treatment, side effects, and the high cost of treatment. Therefore, future research should pay more attention to integrated treatment strategies for AD to improve the treatability and preventability of the disease by combining multiple interventions.

Overall, the research on AD still has a long way to go, but with the in-depth exploration of molecular mechanisms and continuous innovation of technical means, the future is expected to develop more effective diagnosis and treatment methods to improve the quality of life of patients, and reduce the burden of society and families.

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