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A-β Related Pathogenesis of AD Progress of Its Targeted Therapy

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Abstract:

Alzheimer's disease is a common type of dementia in people 65 years of age and older. Tens of millions of people worldwide are living with AD, and the number continues to grow. To date, there are several hypotheses about the pathogenesis of AD, the most widely studied of which is related to the accumulation of Aβ. Currently, there are five drugs in clinical treatment, most of which are inhibitors, as well as monoclonal antibody drugs such as Aducanumab that target Aβ. These drugs can effectively reduce the accumulation of Aβ. However, these drugs have significant side effects and are generally significantly reduced by the end of AD symptoms. This review will summarize the pathogenesis of AD related to Aβ, such as APP and neuroinflammation. This article will also discuss the progress and problems of existing Aβ-based therapies. In addition, this paper will also compare Aβ and Tau proteins to explore better AD treatment methods. These are the basis for further study of the pathogenesis of AD related to Aβ and the development of drugs based on it. Future studies could focus on the direction of immunotherapy targeting Aβ, and apply these drugs to therapies targeting Tau protein.

Keywords: Alzheimer's disease; beta-amyloid protein; Monoclonal antibody; Inhibitors; Therapeutic vaccine; APP.

1. Introduction

Alzheimer's disease (AD) is an extremely common type of dementia, especially in people 65 years of age and older. Tens of millions of people worldwide suffer from AD, including more than seven million in the United States, and the number continues to grow [1]. At the same time, the number of deaths caused by AD continues to increase and became the fifth leading cause of death for people aged 65 and older in 2021. In addition, AD is one of the most expensive diseases in the world, and expensive treatment puts a huge burden on families, societies and governments. Since one of the typical features of AD is the presence of extracellular beta-amyloid plaques containing beta-amyloid protein, it has been hypothesized that the accumulation of beta-amyloid protein is a major factor in the disease, which is called the amyloid hypothesis [1].

Amyloid beta (Aβ) precursor proteins (APP) are processed by β and γ secretase complexes to produce β amyloid peptide [2]. Some studies have suggested that Aβ accumulation is a possible factor in the loss and death of dendritic spines, hippocampus, and entorhinal cortex [3]. Because these areas are closely related to human learning and memory, the learning and memory modules of the brain become vulnerable and decline the most in AD [3]. In addition, Aβ deposits occur at the blood vessel level in most Alzheimer's patients in the form of cerebral amyloid angiopathy [2]. This results in impaired blood-brain barrier (BBB) structural integrity, abnormal clearance of Aβ and further Aβ accumulation [2]. However, the pathogenesis of AD has not been conclusively concluded. In past studies, targeting Aβ is an extremely important direction of AD treatment, but many targeted drugs have not achieved clinical success [4]. These drugs are mainly divided into two types: inhibitors and monoclonal antibodies (mAbs) [4]. Recently, the FDA approved mAb called Aducanumab that targets Aβ aggregates to reduce early-stage Aβ plaque levels [5]. This proves that Aβ and amyloid-based therapies can have an impact on AD.

This review will summarize the pathogenesis of AD related to Aβ, and discuss the progress, problems, and prospects of existing amyloid-based therapies. This is the basis for further research on the pathogenesis of AD related to Aβ and the development of targeted therapies based on it and also provides the basis for the study of more neurodegenerative diseases and drug development with Aβ.

2. Aβ related pathogenesis of AD

2.1 Aβ and APP

The amyloid hypothesis is the leading hypothesis that APP causes AD. Although most of the functions of APP

and Aβ have not yet been discovered, this hypothesis suggests that APP mutation will increase the accumulation of Aβ, and excess Aβ will further lead to neuronal death and synaptic dysfunction [6]. For example, excitotoxicity occurs when N-methyl-D-aspartate (NMDA) receptors are activated by Aβ, one of several mechanisms that lead to neuronal death [7]. There are three main subtypes of APP, APP695, APP751 and APP770, which are sequentially cut to produce Aβ [8]. APP is first cleaved by β-secretase and then further cleaved by γ-secretase by two remaining membrane-associated carboxyl terminal fragments (CTF) of APP: αCTF and βCTF, and finally Aβ is produced [8]. In addition, apps can also be directly cut by caspase to produce neurotoxic fragments, leading to harmful cascades [8].

2.2 Mitochondrial dysfunction and oxidative stress

Due to the high metabolic demand of neurons, many mitochondria are needed to maintain synapses, and the central nervous system consumes a large amount of oxygen, so high concentrations of metabolic by-product reactive oxygen species (ROS) are accumulated. Mitochondria and the central nervous system are also worn down by these toxic high concentrations of ROS during the life cycle [9]. Therefore, some studies believe that the pathogenesis of AD is affected by the accumulated oxidative stress mechanism. Mitochondrial DNA (mtDNA) is severely damaged by ROS, and these mitochondrial defects greatly reduce the function of neurons, thereby increasing the incidence of AD. At the same time, damaged DNA also raises the level of free radicals, which further damage mtDNA [9]. In addition, according to the mitochondrial cascade hypothesis, mitochondrial defects can cause APP to run out of control, produce Aβ oligomers that can form plaques, accelerate the rate of human aging, and thus make humans more susceptible to AD [7].

2.3 Neuroinflammation

Inflammation is an important factor in the development of numerous neurodegenerative diseases, including AD, which is more likely to occur in people who have inflammation. Studies have shown that the accumulation of Aβ and neuronal damage can be affected by inflammation and become worse. The onset of neuroinflammation is facilitated by a process of reactive glial proliferation that occurs when astrocytes and microglia are activated. Studies have shown that microglia, the brain's first line of defense, can be activated by APP and Aβ to release toxic cytokines [10]. This not only promotes the expression of inflammation, but also produces ROS that can lead to neurotoxicity and increase the prevalence of AD [10]. In addition to releasing gamma-secretase and using gamma-secretase to cleave APP to produce Aβ, astrocytes can also help prolong neuroinflammation, which can trigger AD [10].

Whether it's APP, mitochondrial dysfunction, or neuroinflammation, these symptoms produce Aβ and accumulate Aβ, making A person more susceptible to AD. It can be seen that the accumulation of Aβ is an extremely important factor in the initiation of AD. Therefore, in clinical treatment, it is necessary to use inhibitors to inhibit the production of Aβ and reduce the accumulation of Aβ. Immunotherapy with mAbs and specific vaccines can also be used to reduce the accumulation of Aβ.

3. A-β-based targeted therapy

3.1 Monoclonal antibody (mAbs)

mAbs is widely used in passive immunotherapy, where it can directly target Aβ for inhibition. The concentration of Aβ can be reduced by the interaction of mAb and Aβ, allowing Aβ to flow out of the brain through A concentration gradient created by BBB. There is a lot of research on mAbs, of which Aducanumab, as a recombinant human immunoglobulin monoclonal antibody, is the first drug approved for clinical treatment. Aducanumab targets the N-terminal of Aβ and binds to Aβ so strongly that microglia can also be gathered at the site of Aβ aggregates, so that toxic substances can be cleared by phagocytosis [11]. Studies have shown that plaque is successfully reduced under the action of Aducanumab. In addition, Lecanemab, a humanized IgG1 version of mouse mAb158, is also an approved mAb for clinical treatment [11]. Lecanemab can reduce the amount of Aβ in the brain and provide effective treatment. According to the results of the study, there were no serious side effects in patients receiving Lecanemab, so it is a safe drug. But these immunotherapies, which combine Aβ and mAbs, are only effective in the early stages of AD symptoms [12]. Therefore, mAbs needs to be combined with other therapies for better treatment. For example, since it is the ability of mAb to cross BBB and penetrate parenchyma to generate Aβ concentration gradient to clear plaques, it has been proposed that mAb can be coupled with PEGilate liposomes, which not only maintains the binding ability of Aβ to mAbs, but also improves the clearance ability of macrophages [13].

3.2 Inhibitors

In mild to moderate stages of AD symptoms, cholinesterase inhibitors are often used in current clinical treatment. These cholinesterase inhibitors include galantamine, capalatine, and tacrine, which prevent the breakdown of acetylcholine [12]. Because acetylcholine is an important chemical in the memory and thinking areas of the brain,

some behavioral and cognitive symptoms can be alleviated and controlled with cholinesterase inhibitors. In addition, Donepezil, also a cholinesterase inhibitor, can be used to treat moderate to severe AD symptoms [12]. In addition to these inhibitors that are already in clinical use, there are two potential investigational inhibitors: BACE1 inhibitors and gamma-secretase inhibitors (GSI). BACE1 is an enzyme used to produce Aβ, and inhibiting its activity can reduce the accumulation of Aβ [11]. However, BACE1 inhibitors have not been approved for clinical treatment due to difficulties in occupying the entire large active site and easy to cause side effects. GSI also inhibits Aβ production. However, the processing and production of other proteins can also be inhibited by GSI, causing great side effects, such as the Notch receptor family. Notch mediates critical signaling during development and in adults, and since GSI may select proteins other than APP for inhibition, interference with Notch signaling has been one of the side effects of GSI [14]. The most promising GSI for now is Avagacestat over Notch for APP, but it still causes gastrointestinal and dermatological side effects. To date, no GSI has successfully passed clinical trials.

3.3 Therapeutic vaccine

In addition to passive immunization using mAbs, vaccines also make active immunization one of the most promising ways to treat AD. According to the data, the accumulation of Aβ is reduced after vaccination with A vaccine made from Aβ peptide. The first vaccine to go through clinical trials, AN1792, made from A synthetic full-length Aβ42 peptide, slowed cognitive decline, but it also caused aseptic meningoencephalitis in some recipients [14]. So the development of a vaccine to synthesize peptides failed. To overcome these problems, the development of DNA vaccines encoding Aβ is also on the agenda. According to some recent studies, Aβ accumulation levels in mice with AD were successfully reduced by the DNA vaccine encoding Aβ without any significant adverse effects [15]. However, due to DNA vaccination, the production of human antibodies is affected and reduced, so it is necessary to enhance the production of specific antibodies with vaccine-booster regimen, such as Aβ1-42 trimer DNA vaccine [15]. These Aβ1-42 trimer DNA vaccines can not only prevent the onset of AD, but also effectively slow down the symptoms and progress of AD.

4. Problems of treatment

4.1 Insufficient specificity

However, there are still many problems in the research of anti-Aβ therapy. The first is the lack of specificity of the drug. This problem is very common in inhibitor studies, both in BACE1 inhibitors and in GSI studies. For GSI, because gamma-secretase has dozens of substrates and lacks substrate specificity, it often causes toxicity during inhibition. The most important one is that GSI inhibits the Notch receptor family, especially Notch-1, while inhibiting APP [11]. Notch-1 cleavage is reduced by inhibition of GSI, which results in toxicity and disruption of the basic signaling of the Notch-1 receptor [11]. Similarly, BACE1 inhibitors face similar obstacles. For example, BACE2 and BACE1 are closely related homologs, but unlike BACE1, which is an enzyme that produces Aβ, BACE2 protects nerves and reduces neuronal death. The inhibition of BACE1 inhibitors works on BACE1 as well as BACE2, which to some extent inhibits the production and accumulation of Aβ but also inhibits neuronal protection, and even leads to some side effects such as off-target Aβ-targeting antibodies [11]. In addition, studies have shown that some antibodies reduce the accumulation of Aβ while also causing some neuron synapses to be swallowed. In these cases, the symptoms of AD do not improve but become worse.

4.2 Side effects

Second, the side effects of many of the treatments being studied can outweigh their benefits, making the process complicated and difficult. Three people died during the donanemab Phase III trial and two others died during the lecanemab open-label expansion, and their deaths were associated with amyloid-related imaging abnormalities (ARIA) as a side effect [16]. In addition, equally common side effects are infusion related reactions, and the occurrence of functional unblinding is strongly related to its effect on ARIA [16]. These side effects eventually lead to more serious consequences than AD, seriously endangering human health.

4.3 Lack of accurate animal models

Finally, the pathogenesis of AD is very complex, involving many factors such as genetics, environment and lifestyle, which makes it difficult to determine the exact cause and effective treatment. In order to better study the pathogenesis and treatment of AD, animal models are often widely used to summarize the course of AD. However, there are only mice models with early familial AD disease, and the mouse models with delayed sporadic AD, which are more complex and affected by more factors, are not able to respond and express effectively and accurately [11]. In addition, some systems in animal models, such as the immune system, are very different from those in humans, so some factors that may contribute to the onset of AD in humans, such as neuronal death, are difficult to accurately study in animal models [11]. These factors cannot

be accurately expressed and studied, so the study of the pathogenesis of AD is still at the conjecture level, there is no definite mechanism, and many treatment plans are still being explored and designed, and there is no practical development and experiment.

5. Tau protein and Aβ

Aβ and Tau proteins are two of the most important factors in the pathogenesis of AD, and two of the most important conjectures. Among them, Tau is a kind of microtubule-associated protein, and the excessive phosphorylation of Tau protein will produce NFT, thereby causing AD disease. Existing studies have shown that Tau protein and Aβ interact with each other in the pathogenesis of AD. For example, Tau protein is hyperphosphorylated by Aβ-enhanced GSK-3β and CDK-5 activity, which further leads to the formation of NFT and neuronal degeneration [17]. In addition, GSK-3β and CDK-5 activated by Aβ also promote the formation of Tau oligomers, causing damage and degeneration of neurons. Conversely, the toxicity of accumulated Aβ is also influenced by Tau protein, which plays an important role in the induction mechanism of Aβ [17]. In addition, mitochondrial damage and mitochondrial dysfunction are also the result of the co-production of Aβ and Tau proteins. Mitochondrial function in the human brain is impaired by the fragmentation of Tau protein and induced by Aβ, which is produced by overexpression of APP [17]. At the same time, mitochondrial toxicity is also released from the N-terminal Tau fragment, and mitochondrial function is thus impaired [17]. According to studies, the cognitive ability of AD patients continues to decline due to the interaction of Aβ and Tau proteins, and therapies targeting Aβ or Tau proteins alone have not achieved good clinical results [17]. So treatments that can interfere with the interaction between the Aβ and Tau proteins need to be investigated. For example, the production of GSK-3β and CDK-5 inhibitors induced by the hyperphosphorylation of Tau protein induced by Aβ activation can be studied. However, until now, no inhibitor has been proposed that can inhibit both Aβ induction and Tau hyperphosphorylation [17]. This may be due to the fact that pathways containing multiple targets cannot be inhibited simultaneously by inhibitors.

6. Conclusions

So far, there are many hypotheses about the pathogenesis of AD related to Aβ, such as APP, mitochondrial disorders, and neuroinflammation. Because of these assumptions, Aβ is considered to be one of the most important factors in the development of AD, so it is often used as an important target in treatment programs. However, due to the enormous complexity of the pathogenesis of AD itself, and the significant side effects of drugs, the vast majority of therapies targeting Aβ have failed. In addition, according to the results of the study, Tau protein and Aβ interact to affect the onset of AD. The summary of the pathogenesis of AD related to Aβ, the analysis of the current status of therapeutic research and the listing of the role of Aβ and Tau proteins in this review all point out that more accurate animal models are needed for the simulation of the disease and drugs that target both Aβ and Tau proteins should be studied, so as to better help slow the progression of AD disease. This also provides A focus for subsequent research: targeting Aβ immunotherapy, whether active or passive immunotherapy, and targeting these therapies against Tau protein. Of course, the Aβ-based pathogenesis and factors mentioned in this review are only A few of many factors, and many other factors are associated with the onset of AD. The absence of these factors in therapeutic studies may result in a suboptimal treatment for AD or the failure of the entire trial. In addition, the current difficulties in drug development are not fully explained in this review, and more issues such as the variability of AD, as well as research and development costs and funding may need to be considered in actual research. It is hoped that targeted research and accurate model simulation can be carried out for different types of AD incidence to improve the success rate of clinical trials. At the same time, it is also hoped that it can pave the way for further accurate research on the pathogenesis of AD related to Aβ and the development of targeted therapies based on it, so that more research and drug development of Aβ-related neurodegenerative diseases will become easier and more promising.

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