Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/77/2024.LA19840

Alzheimer disease: Mechanism and treatments

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Abstract. Alzheimer's disease, AD, has been a difficult problem for relevant experts and patients since its discovery. As a neurodegenerative disease, it can lead to cognitive decline and seriously affect the patient's life. In recent years, with the aging of the world's population, and the combination of various factors, the prevalence of Alzheimer's disease worldwide has been increasing, causing widespread concern in society. The pathogenesis of Alzheimer's disease is complex, which is one of the reasons why it is difficult to find an effective treatment until now. Extracellular plaques and intracellular tangles are more important causes of disease. They block communication between nerve cells and cause the death of nerve cells. It makes the patient's brain atrophy, neuroplasticity decline, and ultimately more severe cognitive decline. Most of the current treatments for Alzheimer's disease point to the formation path of plaques and tangles. There are also monoclonal antibody drugs that are more directly directed against plaques. However, almost all of these drugs have disadvantages such as insufficient efficacy or more serious side effects. Most of the drugs used to treat AD can only relieve pathological processes such as cognitive decline in patients, and there is a lack of treatment for patients with more severe symptoms. Most of the current research has been carried out from both pathogenesis and drug development. This article will also review the progress of AD and related research from these two aspects, respectively.

Keywords: Alzheimer Diseases, Aβ plaques, Amyloid Precursor Protein, Lecanemab, Donanemab.

1. Background

As early as 1907, a German physician reported a disease that occurred in a 51-year-old woman, although her symptoms were very similar to those of a series of neurological disorders that had been found at that time, including Alzheimer's disease, including rapid deterioration of memory, accompanied by more pronounced mental disorders. But the onset of Alzheimer's disease is mostly after the age of 65, and her unusual onset, as well as the brand-new pathology found in her, neuronal fibrillary tangles (NFT), have attracted the attention of scientists. Eventually, the disease was named after a German doctor. That is, Alzheimer disease (AD) [1].

Alzheimer's disease is a neurodegenerative disease with some heritability, characterized intracellularly by Tau-containing neurofibrillary tangles and extracellularly by β-amyloid (Aβ) plaques. Most AD patients experience short-term memory difficulties, as well as very severe amnesic cognitive impairment. A small number of patients, in contrast, present with non-amnesic cognitive impairment. Some patients also have language and visuospatial processing dysfunction.

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At present, AD is found to have some heredity, which can be divided into three conditions: gene mutation and special allele, as well as epigenetic modification. Among them, the more important gene mutations include the mutation of amyloid protein (APP) gene, as well as the mutation of presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes, which will greatly increase the probability of early-onset AD and have a higher familial inheritance. For the ε4 allele on the apolipoprotein (APOE) gene, the data suggest that its presence significantly increases the probability of disease in late-onset AD. At the same time, the ε2 allele on the APOE gene corresponds to a lower risk of AD. DNA methylation as well as histone modifications are also an aspect that cannot be ignored in the causes of AD[2]. Environmental factors as well as the patient's personal lifestyle habits, such as smoking and excessive alcohol consumption, may increase the risk of Alzheimer's disease in this way.

In China, and even the world, Alzheimer's disease has been a difficult to ignore health and even social problems. In Figure 1, it can be seen that just in the last two decades, there has been an alarming increase in the prevalence of and deaths from AD compared to traditional fatal diseases such as heart disease and cancer. However, there is a lack of more effective treatment so far. The increase in the number of patients is not a small challenge for the existing medical resources, as well as the economic overhead required for the corresponding treatment. Its imperfect diagnostic and therapeutic means make some people try to obtain improper benefits from them. It also has some negative effects on society. Most of the current drugs for Alzheimer's disease are aimed at relieving existing symptoms, using drugs such as acetylcholinesterase inhibitors, and NMDA receptor antagonists to improve the homeostatic imbalance of intersynaptic neurotransmitters. These drugs have had little success in the case course of AD. Although little progress has been made in drug development directly targeting Tau tangles and Aβ plaques, it has still not been widely used[4]. Therefore, the current treatment of Alzheimer's disease can only play a role in delaying the deterioration of the disease. This will undoubtedly subject the patient to more unnecessary suffering and subject the patient's family to a heavier financial burden. Therefore, it is necessary to study more effective and economical drugs and treatments for Alzheimer's disease.

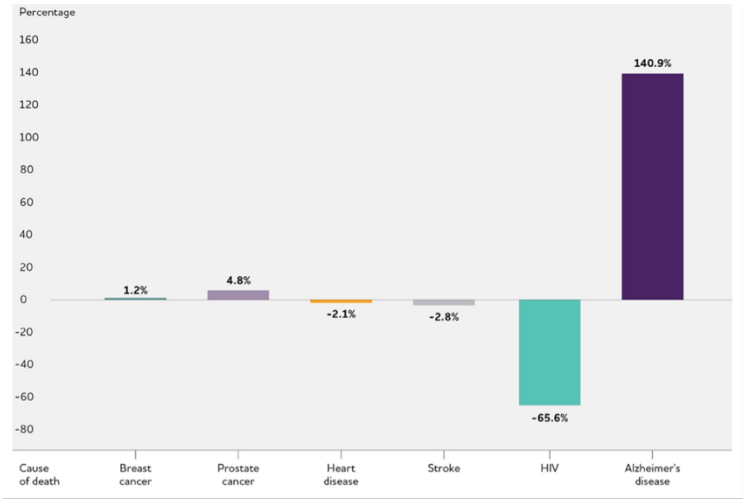

Figure 1. Percentage changes in selected causes of death all ages between 2000 and 2021[5].

The risk of Alzheimer's disease gradually rises with age[3]. Over the age of 65, the prevalence of patients, as well as the impact of Alzheimer's disease on the health and living conditions of patients have been significantly improved. And when statistics come to 85 years of age and older, almost one in four older adults is suffering from AD. The data in Figure 2 shows that from 2020 to 2060, the number of people with AD is expected to double, and that people aged 85 and older will be one of the most significant contributors to this increase. Such a prevalence is undoubtedly a horrible but unacceptable fact for an aging society worldwide[3].

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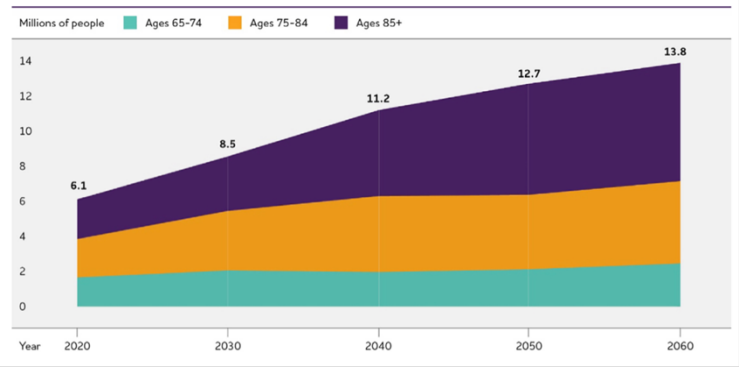

Figure 2. Projected number of people age 65 and older (total and by age) in the U.S. population with Alzheimer's Dementia, 2020-2060[5].

The risk of AD is significantly higher in women than in men, with women aged 45 and 65 years having nearly twice the risk of AD compared to men in the data in Figure 3. The current study suggests that Follicle-stimulating-hormone (FSH) is likely to be responsible for the results [6]. However, at the same time, the different physiological structures of men and women, as well as the different roles assumed in society, and even the gap in education between men and women in the past, may directly or indirectly lead to differences in prevalence.

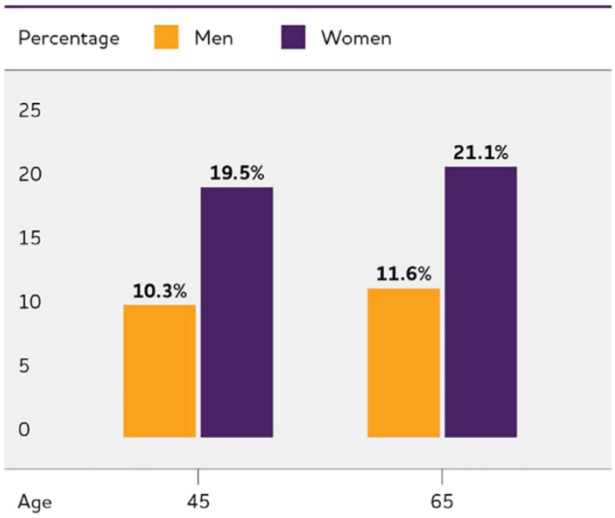

Figure 3. Estimated lifetime risk for Alzheimer's Dementia, by sex, at ages 45 and 65[5].

Globally, there appears to be some association between socio-demographic index (SDI) and the incidence of Alzheimer's disease. Specifically reflected in the fact that areas with higher SDI tend to have higher AD prevalence, while areas with lower SDI generally have lower AD prevalence[7]. Therefore, regions with high SDI, that is, countries or regions with higher levels of social development, should invest more attention and financial support to develop more effective means of diagnosing and treating Alzheimer's disease.

2. Pathogenesis

The pathogenesis of AD is more complex and mostly revolves around the generation of tau-tangles and A-beta plaques. The study of the formation process of these two important substances is undoubtedly an important idea to overcome Alzheimer's disease.

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For Aβ plaques, it first originated from the amyloid precursor protein (APP) on the cell membrane of cranial nerves. APP plays an important role in neuronal growth, as well as during repair after injury. During its degradation, it is normally cleaved by α-secretase and γ-secretase to produce soluble APPα (sAPPα) which in turn is broken down. There is also β-secretase (BACE1) in the human body, which cleaves APP with γ-secretase to produce insoluble amyloid-β (Aβ), which forms plaques in the aqueous extracellular environment, which in turn blocks information transmission between nerve cell synapses, thereby affecting functions such as memory in the brain. It causes an immune response and produces inflammation. The aggregation of these plaques leads to Amyloid Angiopathy in cerebral vessels and disrupts the blood-brain barrier.

The formation of Aβ plaques outside the cell also promotes the transport of kinase carrying phosphate groups to Tau. Tau is a protein that supports the action of tubulin, which helps maintain the cytoskeleton of nerve cells and allows them to function normally. A large number of kinases carrying phosphate groups can lead to hyperphosphorylation of Tau. Hyperphosphorylated Tau undergoes structural changes that render it unable to continue to support tubulin and cluster together to produce tau-tangles. Microtubules lost their original ability to support neuronal cells, causing damage to neuronal cell structure and loss of information transmission. This affects normal functions such as memory in the brain.

γ-secretase, which is indispensable in the cleavage of APP, is a complex of a variety of substances, of which presenilin is its important catalytic subunit, which contains an active site and can be directly involved in catalytic reactions. Therefore, it plays a more critical role in the cutting of APP [8]. The proteins encoded by the PSEN1 and PSEN2 genes are presenilins (presenilin 1, presenilin 2). Mutations in the PSEN1 and PSEN2 genes cause changes in the structure of presenilins, which in turn affect γ-secretase properties. The end result is a change in the ratio of Aβ40 to Aβ42, the two products produced by γ-secretase to β-secretase cleavage of APP, as reflected by a large increase in the production of Aβ42. Among them, Aβ42 has two more amino acids than Aβ40, so they would be more likely to aggregate to form plaques, thereby disrupting the information transmission path between synapses[9]. Therefore, it is generally believed that Aβ42 is more neurotoxic than Aβ40. The increased proportion of Aβ42 caused by mutations in the PSEN1 and PSEN2 genes can lead to the formation of more plaques, which in turn increases the risk of Alzheimer's disease

In recent years, many studies have shown that APOE ε4 allele is also associated with Alzheimer's disease, including increasing hyperphosphorylated tau in vivo, and promoting the formation of plaques by Aβ42 polymerization, which reduces the proportion of Aβ42 to Aβ40 [10]. APOE ε4 has been shown to bind to the LilrB3 receptor and further activate microglia [11], a process that is likely to trigger an inflammatory state in the body, which may lead to nerve tissue damage and also affect Aβ clearance in the long-term inflammatory state. The structure of APOE can inhibit the activity of γ-secretase, but its lower inhibitory ability compared with its allelic variants APOE ε2 and APOE ε3 means that people with the APOE ε4 allele may produce more Aβ in vivo, which in turn produces plaques and ultimately leads to symptoms of Alzheimer's disease.

3. Treatments

3.1. Acetylcholinesterase inhibitor

As a neurotransmitter, acetylcholine plays a role in information transmission between synapses. Acetylcholinesterase can specifically hydrolyze acetylcholine, thereby terminating the role of neurotransmitters on the postsynaptic membrane and helping to maintain synaptic homeostasis in normal subjects. For AD patients, due to extracellular production of Aβ plaques blocking the transmission of inter-synaptic neurotransmitters, it is impossible for neurons to communicate substances and information normally. At this time, normal activity levels of acetylcholinesterase in AD patients will make the synaptic cleft of acetylcholine further hydrolysis, so that the synaptic transmission of excitation is more blocked. Therefore, the use of acetylcholinesterase inhibitors can improve the condition to some extent, so that the synaptic homeostasis of nerve cells in AD patients can be repaired

DOI: 10.54254/2753-8818/77/2024.LA19840

to some extent. More acetylcholinesterase inhibitors, including Donepezil, Galantamine and Rivastigmine, are currently used, which reversibly inhibit the activity of acetylcholinesterase by specifically binding to the active site on acetylcholinesterase, that is, after a period of time, the inhibition will decrease spontaneously, thus making the use of this class of drugs safer and sensitive[12]. It can relieve the symptoms caused by AD to some extent in the early stage of AD. For most patients, acetylcholinesterase inhibitors do not significantly improve cognitive, language and learning dysfunction. However, it can alleviate the deterioration of the overall health status and cognition of patients to some extent. And it can reduce the risk of death to some extent in patients with more severe AD conditions[12]. It is worth mentioning that the use of acetylcholinesterase inhibitors is often accompanied by nausea, vomiting, diarrhea and loss of appetite side effects, which will affect the quality of life of patients to some extent. However, taken together, the use of acetylcholinesterase inhibitors has positive implications for AD patients.

3.2. NMDA receptor antagonist

In the pathology of AD, Aβ plaques inhibit the reuptake process of glutamate. It allows glutamate to bind in excess to NMDA receptors (N-methyl-D-aspartate receptors) distributed in the central nervous system, resulting in excessive activation of NMDA receptors. It allows excessive calcium ions to enter neurons, resulting in damage to the cellular structure of neurons and even death. The process leads to reduced synaptic plasticity, manifested as impaired learning and memory in patients. The widely used class of NMDA receptor antagonists is currently mainly Memantine. It can act by binding to NMDA receptors, alleviating the excessive influx of calcium ions resulting from the massive binding of glutamate to NMDA receptors. Memantine can also reduce Aβ levels to some extent. Clinical data show that Memantine has a certain therapeutic effect on patients in the middle and late stages of AD pathological process, which is reflected in the recovery of patients' expression, learning and memory ability, as well as the recovery of patients' self-care ability in life. The role of AD is not evident in patients with earlier AD progression. Of note, Memantine also has an excellent effect in relieving AD symptoms when used in combination with acetylcholinesterase inhibitors[13]. Memantine has fewer side effects, and only a small proportion of people who receive Memantine experience side effects including dizziness, as well as dizziness, with less impact on physical health [13]. The appropriate use of NMDA receptor antagonists with acetylcholinesterase inhibitors is of some help in restoring and maintaining substance balance in AD patients, as well as alleviating further development of pathological processes

3.3. BACE1 inhibitor

In the pathogenesis of AD, the formation of Aβ plaques is a more critical step. B-secretase (BACE1) and γ-secretase together cleave APP to produce insoluble β which in turn forms extracellular plaques. During normal APP breakdown and recovery, it is α-secretase and γ-secretase that cleave APP to produce soluble substances. During the pathogenesis of AD patients, the increased expression and activity of BACE1, will lead to the increased formation of Aβ plaques. Therefore, appropriate use of BACE1 inhibitors inhibits the activity of BACE1 by specifically binding to BACE1, so that APP is more decomposed into substances that can be normally recovered by the human body. It can alleviate the symptomatic deterioration of AD to some extent. And the number of Aβ plaques was reduced. However, it is worth noting that BACE1 acts not only as a tool for cleavage of APP in the human body. It is also involved in the cleavage of substances including insulin receptors, receptor, nerve growth factor (NGF), etc. [14]. This means that BACE1 activity and expression not only affect substances associated with the pathological process of AD, but also are associated with human metabolism, maintenance of nervous system function, and immune response. This makes BACE1 inhibitor drugs face many problems in the treatment of AD. The first is that the widespread distribution of BACE1 in the body makes it difficult to determine the dosage and administration of BACE1 inhibitors. Smaller dosage will lead to insufficient efficacy, while excessive use will lead to other functions of BACE1 in the body, resulting in more problems. Second, BCAE1 inhibitors can only slow down the production of Aβ plaques to some extent,

DOI: 10.54254/2753-8818/77/2024.LA19840

but for patients who already have a large number of Aβ plaques accumulated in the body in the middle and late stages of AD pathology, the therapeutic effect is poor. Third, a series of side effects including hepatotoxicity problems occur due to insufficient studies on BACE1 function and mechanism. These have led to the development of BACE1 inhibitor drugs that are often forced into trouble after clinical trials. However, it is anticipated that BACE1 is one of the important targets for the treatment of AD. More progress may be made in the development of BACE1 drugs after more understanding of the function and mechanism of BACE1 in the human body.

3.4. Monoclonal Antibody

Among the drugs for the treatment of AD, monoclonal antibody drugs have certain advantages due to their ability to directly reduce the level of Aβ plaques rather than acting indirectly by regulating other substances during their formation. Current monoclonal antibodies for the treatment of AD mainly include aducanumab, lecanemab and donanemab. Among them, Lecanemab mainly binds protofibrils formed after APP is cleaved to produce Aβ, relying on the process to inhibit its subsequent formation of plaques, so as to achieve the purpose of reducing the level of Aβ plaques in patients[15]. Donanemab, on the other hand, specifically binds N3pG-modified Aβ plaques and directly clears Aβ plaques using microglial phagocytosis by causing an immune response. It is worth mentioning that Aβ, which forms plaques in the human brain that in turn lead to AD symptoms, contains N3pG modifications. The nature of binding to this specially modified Aβ plaques allows Donanemab to have superior specificity and better clear Aβ plaques from the brains of AD patients[16]. Aducanumab binds to both Aβ fibers before the formation of plaques, but also binds to formed Aβ plaques and elicits an immune response clear Aβ plaques to function , and the mechanism of action of this part is more similar to that of Donanemab[17]. However, compared with Donanemab, aducanumab lacks specificity for the clearance of Aβ plaques, which may trigger some additional side effects and is reflected in clinical trials.

In clinical trials, Lecanemab and Donanemab have shown good results and produced more convincing data than aducanumab. Among them, Lecanemab achieved a gap of -0.45 (1.21 in the Lecanemab group and 1.65 in the placebo group) in the CDR-SB value of cognitive function in responding patients [15], indicating that Lecanemab can significantly slow down the cognitive decline experienced by AD patients. At the same time, Lecanemab achieved a change of -55.48 Centiloids in the Centiloids value of Aβ levels, compared with the data of the placebo group of 3.64 Centiloids [15], which demonstrated that Lecanemab was effective in eliminating Aβ plaques in AD patients. In Donanemab's clinical data, Donanemab's iADRS, which reflects cognitive and functional impairment in patients, achieved a change of -6.02 for Donanemab in patients with moderate to low tau values, compared with -9.27 for placebo, and -10.2 for mixed patients, compared with -13.1 for placebo. Such results indicate that Donanemab can better alleviate cognitive decline in patients with different tau values [18]. The clearance effect of Donanemab for Aβ plaques is particularly prominent, and clinical data indicate that for patients with low initial levels of Aβ, Donanemab has a 40% probability of reducing their Aβ levels to normal values, that is, lower than 24.1 Centiloids[19].

Although monoclonal antibodies have better therapeutic effects on AD than other types of drugs, their side effects are also difficult to ignore. Amyloid-Related Imaging Abnormalities, ARIA is the most significant side effect, which may cause a range of symptoms including headache, confusion, but also the probability of causing epilepsy or even death. Approximately 12.6% of patients receiving Lecanemab in clinical trials developed ARIA[15]. For aducanumab, this figure reached 35.2%. Clinical treatment with Donanemab also yielded an ARIA rate of approximately 26.1 – 30.5% [19]. At present, the high incidence of ARIA has led to a certain stagnation in the progress of monoclonal antibody drug development. In subsequent studies, the mechanism of ARIA and the use of monoclonal antibodies for the treatment of AD are additional monitoring and treatment tools that should be taken, and should be one of the directions of drug developers and medical workers.

DOI: 10.54254/2753-8818/77/2024.LA19840

4. Conclusion

The current pathogenesis of AD has been relatively clear, but there is still a lack of progress in the current research on the association between the two pathogenic pathways, Aβ plaques and tau tangles, and the possible interaction mechanism. At the same time, the materials and processes designed on these two pathogenic pathways are also more complex, and it may provide new ideas for their in-depth study, diagnosis, treatment, and prevention and treatment of AD.

The current problem of synaptic homeostasis imbalance in AD patients. The problem with the use of acetylcholinesterase inhibitors and NMDA receptor antagonists is the lack of pertinence. It can only improve the symptoms caused by AD to some extent, but it is less effective in slowing down the progression of AD pathology. However, considering these two treatment ideas has shown a certain effect in clinical trials, and the possible side effects are also relatively small. These two classes of drugs may be considered as adjuncts to other more specific drugs for the treatment of AD. It can further reduce the impact of AD on patients' brain function as well as daily life.

Although BACE1 inhibitors can limit the formation of Aβ plaques, the lack of understanding of other functions of BACE1 in the human body makes BACE1 inhibitors face dosage and administration problems during their use. The monitoring of patient status and timely management may improve the use of BACE1 inhibitors to some extent, but the lack of therapeutic ability for patients with advanced AD pathology is an insurmountable defect. If existing AD diagnosis and prevention means can be improved, BACE1 inhibitors may obtain wider use space and better therapeutic effect.

Monoclonal antibody drugs are currently a class of drugs that hope to improve the condition of AD patients. Its specificity, as well as its direct nature for the clearance of pathogenic substances, makes this class of drugs promising. Among them, Donanemab has made a major breakthrough in specificity. However, the side effects of ARIA that are difficult to ignore will be a difficult problem to prevent the further development of monoclonal antibody drugs. Further improvements in monoclonal antibodies, the discovery of more specific recognition sites for pathogenic substances, and better control and prevention of ARIA will be breakthroughs in the future progress of monoclonal antibody drugs in the treatment of AD.

AD is a disease that afflicts nearly 60 million people worldwide, and the prevalence is still rising. Research on it is also evolving, and it is believed that in the future, with a more meticulous understanding of AD, as well as improvements and innovations in existing treatments, humans will eventually have the opportunity to completely cure and prevent AD.

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