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Research Progress and outlook of drugs for the treatment for Alzheimer's disease

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Abstract:

As the global population is aging at an increasingly rapid rate, AD has become an important disease affecting the health of the elderly in today's world and has attracted the attention of many experts. AD is a neurodegenerative disease characterized by progressive cognitive decline, manifested by deterioration of memory, learning and daily living skills. If the disease is not controlled, patients will develop dementia symptoms. Although AD cannot be completely cured at this time, a combination of pharmacologic and non-pharmacologic treatments are currently available to alleviate symptoms. Pharmacological treatment may include cholinesterase inhibitors (ChEIs) and NMDA receptor antagonists. Non-pharmacological treatments include psychotherapy, cognitive training and life skills exercise. This paper now reviews the mechanisms, applications and side effects of the corresponding drugs that have been used to treat AD, and analyzes the emerging AD treatments, with a view to providing a reference for the research of new AD therapeutic drugs.

Keywords: Alzheimer's disease; cholinesterase inhibitors; research progress.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease (NDD)with an insidious onset and is the most common type of dementia, characterized by cognitive deficits, mental and behavioral abnormalities, and reduced social functioning. The incidence of AD increases with age, with a prevalence rate of 15% in people over 65 years old, and up to 45% when they reach 85 years old[1]. The earliest stages often begin with progressively worsening forgetfulness, which is usually not easy to detect if not paying attention. AD currently affects 50 million people worldwide, and as aging deepens, the number of people with the disease continues to grow, bringing a heavy burden to society and families, and AD is gradually becoming one of the focuses of social concern.

At the same time, the treatment of AD has become a focus of attention. Traditional treatment for AD primarily focuses on managing symptoms, as there is no cure yet. Several medications have been invented out However, until now, only few kinds of drugs have been approved by FDA for the treatment of AD, for example, ChEIs, N-methyl d -aspartate (NMDA) re-

ceptor antagonist and Anti-amyloid monoclonal antibodies (mAbs) [2]. Moreover, Behavioral and Psychological Symptoms Management, Supportive Therapies and Cognitive Stimulation Therapy (CST) all have been used to help release the symptoms of AD. All of these treatments only slow the worsening of AD symptoms, but do not stop the progression of the disease.

However, the side effects of Alzheimer's medications should not be underestimated. In the United States, Lencanemab, one kind of Anti-amyloid mAb, is already allowed for the treatment of AD [3]. Despite the efficacy of Lencanemab, there are some side effects to be aware of, such as amyloid-related imaging abnormalities-oedema/effusion (ARIA-E) and amyloid-related imaging abnormalities-haemosiderosis/microhaemorrhages (ARIA-H) [4]. Various other drugs can cause side effects, which may irritate the gastrointestinal tract and cause nausea and vomiting, as well as symptoms such as dizziness and headache.

As a result, a large number of drugs targeting other mechanisms of AD bio trajectory for treatment are under development. With advances in medical research, treatments are improving, such as the use of drug combinations and individualized treatments. Emerging therapies mainly include Aβ immunotherapy, Disease-Modifying Therapeutics (DMT), Tau protein vaccines, psycho-behavioral symptom medication and stem cell therapy.

The purpose of this article is to review the drug mechanisms, application effects, side effects and new therapeutic approaches for the treatment of this disease, with a view to contributing to future therapeutic and scientific research on AD.

2. Medications

The goal of pharmacological treatment of AD is to relieve symptoms and slow the progression of the disease. There are only two drugs are approved for the treatment of AD, ChEIs and NMDA. These drugs act by modulating neurotransmitter levels or by affecting the increased excitability of neurons. In addition, neuroprotective drugs and targeted treatments are being developed and studied. These drugs improve cognition, behavior and functioning of Alzheimer's patients to some extent, but they do not cure the disease and are often associated with side effects.

2.1 ChEIs

ChEIs were the first drugs approved for use in the treatment of AD. There are only three ChEIs approved for use by the FDA: donepezil, rivastigmine, and galantamine [5]. These drugs help improve memory and learning function by increasing the level of acetylcholine in the brain by reducing the breakdown of acetylcholine. Donepezil is used in patients with mild, moderate, and severe AD. Rivastigmine is used in mild to moderate AD and may also be used in Parkinson's-related dementia. Galantamine is used primarily in mild to Galantamine is mainly used in patients with mild to moderate AD.

2.1.1 Mechanism of ChEIs

Acetylcholine (ACh) is an important neurotransmitter in the brain responsible for transmitting nerve signals and is associated with memory, learning and cognitive functions. According to the cholinergic hypothesis, AD is due to decreased acetylcholine biosynthesis. People with AD generally have low acetylcholine water, leading to their cognitive decline. Acetylcholinesterase (AChE) is an enzyme responsible for the breakdown of acetylcholine, which terminates acetylcholine signaling in the synapse. Increasing cholinergic levels by inhibiting AChE is considered one of the therapeutic strategies to improve cognition and nerve cell function [6]. By inhibiting the activity of acetylcholinesterase, acetylcholine inhibitors are able to prolong the retention of acetylcholine in the synaptic gap and enhance neural signaling, thereby increasing acetylcholine levels in the synaptic gap. This can enhance the memory and cognitive abilities of Alzheimer's patients to a certain extent. The different cholinesterase analogs vary in structure and duration of action, but they all share the common goal of improving cholinergic neurotransmission and thus alleviating cognitive decline. The application and efficacy of ChEIs in the field of treatment of AD and their efficacy is equally noteworthy.

2.1.2 Application and Effects

Donepezil is considered to be the primary drug for the treatment of AD. Donepezil has been approved by the FDA for the treatment of AD as early as 1996. Donepezil reversibly binds to the enzyme acetylcholinesterase, which inhibits the hydrolysis of acetylcholine, thereby increasing the concentration of acetylcholine in the synapse. Studies have shown that patients taking 5 mg and 10 mg doses of donepezil once a day reduced hippocampal atrophy and lowered Aβ levels [7]. Their cognition, memory, and learning abilities also improved with long-term use. The drug is well tolerated with only mild and transient cholinergic side effects that are related to the gastrointestinal tract and nervous system. It is important to note that donepezil is used to treat symptoms of ADD, such as improving cognition and behavior, but does not alter the progression of ADD. Donepezil not only inhibits cholinesterase but also controls neurotransmitter levels.

Galanthamine not only inhibits the enzyme acetylcholinesterase, but also enhances the neuronal response

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to acetylcholine by modulating nicotinic acetylcholine receptors. The drug is taken twice daily and side effects are usually more pronounced during the dose adjustment period [8]. Studies have shown that galantamine not only improves cognitive function, but also helps alleviate behavioral symptoms such as anxiety and irritability.

Unlike other ChEIs, rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase. This dual mechanism may make it more effective in Parkinson‘s disease. When using these medications, patients will respond differently. Some patients experience significant improvement in their symptoms in the short term, while others experience only slight improvement with long-term use. Overall, ChEIs play an important role in slowing the progression of ADD, but they do not reverse the course of the disease.

2.1.3 Side Effects of ChEIs

On the gastrointestinal side, taking ChEIs increases the reaction of acetylcholine in the gastrointestinal tract, and patients usually experience unpleasant symptoms such as nausea, vomiting and diarrhea. This side effect is usually more pronounced with the initial dose or when the dose is increased.

On the neurological side, ChEIs may also cause a slowing of the heart rate by potentiating the parasympathetic nervous system. This may pose a risk to some patients with a history of heart disease, especially those taking donepezil.

In addition to this, some patients may experience dizziness, insomnia, or unusual dreams after using ChEIs. These adverse reactions are usually mild, but when symptoms are severe, the medication dose may need to be adjusted or changed. A few patients may also experience muscle cramps, fatigue, and respiratory symptoms. Although these side effects are rare, they may affect the daily life of some elderly patients.

2.2 NMDA Receptor Antagonist

The NMDA receptor is an important glutamate receptor. It is widely used in the treatment of diseases related to the central nervous system, such as chronic NDDs (Parkinson‘s, Alzheimer‘s, etc.) NMDA receptor antagonists are used in the clinical treatment of a wide range of disorders by blocking the function of NMDA receptors. Currently, memantine is the only commercially available NMDA receptor antagonist and the first drug approved by the FDA for the treatment of moderate and severe AD. However, NMDA receptor antagonists, despite being available on prescription, are associated with a variety of side effects [9].

2.2.1 Mechanism of NMDA Receptor Antagonists

NMDA receptor antagonists can reduce the excitability of the neurons involved by blocking the ion channels of NMDA receptors and inhibiting the inward flow of calcium ions. According to the site and mode of action, NMDA receptor antagonists can be classified into three categories: competitive antagonists, non-competitive antagonists and inverse agonists.

2.2.2 Application and Effects

AD is a NDD in which overactivation of NMDA receptors leading to neuronal damage and death is one of the key mechanisms. Memantine is a low affinity NMDA receptor antagonist that selectively blocks pathologically overactivated NMDA receptors without affecting normal physiological functions. Memantine is widely used in the treatment of patients with moderate to severe AD. In clinical studies of AD, Memantine has been shown to be more effective in improving patients‘ cognitive functions, especially in memory and language. Meanwhile, its side effects are relatively mild, so this NMDA receptor antagonist has also become one of the standard drugs for the treatment of AD.

2.2.3 Side Effects of NMDA Receptor Antagonist

Chronic or high-dose use of NMDA antagonists may result in cognitive decline, particularly impaired memory, attention, and information processing. Studies have shown that chronic use of ketamine may result in memory loss, inattention, and reduced learning ability [10]. Some patients are able to recover cognitive function gradually after discontinuation of the drug, but irreversible cognitive impairment may occur with prolonged use. Memantine, the standard treatment drug for AD, does not significantly affect patients‘ cognitive function, but may still cause transient cognitive impairment in sensitive individuals.

In conclusion, both drugs are currently the most widely used treatments for AD, and both can reduce the deterioration of memory and cognitive function in Alzheimer‘s patients to a great extent. However, it is undeniable that neither of these treatments can completely cure AD. In addition to this, their side effects vary from person to person and perhaps can have a great impact on the normal life of some patients. So more in-depth studies are necessary at the moment.

3. New Treatments for AD

3.1 DMT

Research suggests that DMT may have a therapeutic effect on AD through a variety of pathways. DMT may promote neuroplasticity and neurogenesis, and act as an antioxi-

dant and cytoprotective. DMT may enhance oxygenation and nutrition of nerve cells by increasing blood flow to the brain. This is particularly important for Alzheimer‘s patients, as decreased blood flow to the brain is closely associated with deterioration of cognitive function. In addition to this, Alzheimer‘s patients are often accompanied by sleep disorders and mood problems such as anxiety and depression. DMT can improve patients‘ mood and sleep through its interaction with other receptors.

3.2 Aβ Immunotherapy

Abnormal accumulation of Aβ is thought to be the central pathomechanism of AD, and Aβ immunotherapy is designed to reduce or remove Aβ plaques from the brain, delaying or stopping NDD. Vaccination with the Aβ vaccine is an active immunization method. After vaccination, the Aβ vaccine stimulates the patient‘s own immune system to produce anti-Aβ antibodies. Early results of the study showed a reduction in Aβ burden, but side effects such as encephalitis occurred. Direct injection of Aβ antibodies is a passive immunization method. After vaccination, Aβ antibodies rapidly clear Aβ [11]. Some clinical trials have shown cognitive improvement, but efficacy is uneven and there are issues with dose optimization and safety. CAD106 is an investigational Aβ vaccine that stimulates the body‘s immune response to Aβ, thereby reducing amyloid plaques in the brain. Ongoing clinical trials have shown a high safety profile and potential efficacy.

3.3 Tau Protein Vaccines

Hyperphosphorylation and tangling of tau proteins in the brains of Alzheimer‘s patients are also key pathological factors, and immunotherapy targeting tau is considered a promising therapeutic strategy. both AADvac1 and Tau protein vaccines belong to the category of Tau-targeted therapies. They both target Tau protein. Slows the progression of Alzheimer‘s disease by reducing the abnormal accumulation of Tau protein. AADvac1 is a vaccine-based active immunotherapy. It reduces Tau protein-associated neurofibrillary tangles formation by inducing an immune response from the immune system. The Tau protein vaccine is a passive immunotherapy in which mAbs are infused directly into the patient‘s body. These antibodies bind only to abnormal Tau proteins, thereby removing them. tau mAbs have the advantage of being highly targeted, recognizing specific Tau protein structures with precision, and are not dependent on a patient‘s own immune system. Clinical trials have shown that AADvac1, an antibody, affects pathological changes in tau proteins with mild side effects. In a 104-week clinical study, researchers calculated the cumulative production of AADvac1-induced anti-tau antibodies in patients during the period [12]. They found a positive correlation between patient antibody production and treatment efficacy, but large-scale trials of AADvac1 are still necessary before they can be put into use. Although a vaccine against tau protein is still in the early stages of research, immunotherapy against tau shows potential to stop the spread of tau protein and reduce nerve damage.

In summary, each of the three innovative therapies for Alzheimer‘s disease has its own focus. DMT focuses on slowing down cognitive deterioration by intervening in the underlying mechanisms of disease progression in order to improve cerebral blood flow. Aβ immunotherapy aims to block the effects of NDD by removing beta amyloid deposits in the brain, which can alleviate symptoms. Tau protein vaccines reduce the accumulation of abnormal Tau proteins mainly by inducing an immune response. Thus, slowing cognitive decline. All three share the goal of slowing the progression of Alzheimer‘s disease, but each acts on different pathologic mechanisms of the disease, with DMT having a broader coverage, while Aβ and Tau vaccines are more focused on specific protein pathologies.

4. Conclusion

In summary, there is no complete cure for AD, but methods such as medication and immunotherapy can prevent the disease from worsening to a certain extent. ChEIs and NMDA receptor antagonists are both in clinical use to improve patient symptoms, but their side effects should not be underestimated. At the same time, new treatments are being researched, such as DMT, Aβ immunotherapy, and Tau protein vaccines. Although these new treatments do not prevent the onset of AD either, they may reduce the side effects of the treatments to varying degrees.

As the incidence of AD rises, research into its treatment remains a pressing issue. While medication is desirable, a way to minimize its side effects has yet to be found. If people with AD can be saved from side effects in the future when they take medication, this will be able to greatly improve their quality of life. So new therapeutic drugs and treatment programs may become the research hotspot for the treatment of AD. Until now, there has been a dearth of research into the drugs and effects associated with this disease area. The emergence of new drugs and therapies will help patients around the world lead happier lives.

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