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Current Understanding and Therapeutic Advances in Alzheimer's Disease

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Abstract. The number of people with Alzheimer's Disease (AD) continues to rise because of global population ages. This disease seriously threatening human health and quality of life. This article systematically reviews the pathogenesis of AD and existing treatments. Amyloid β protein (Aβ) deposition, tau protein abnormalities, neuroinflammatory responses, and acetylcholine dysfunction are the primary pathological mechanisms of AD. These factors work together to can cause the death and dysfunction of neuronal, clinical manifestations memory impairment and disorders of language. There is currently no drug or vaccine that can cure AD, but a variety of treatments have been used to mitigate the spread of the state of an illness and relieve symptoms of patients. The FDA has approved the immunotherapy drugs lecanemab and donanemab targeting Aβ. At the same time, acetylcholinesterase inhibitors are also widely used to treat AD. In addition, psychological interventions such as cognitive stimulation therapy and cognitive rehabilitation also have a positive effect on maintaining patient function. This article aims to help readers get a better comprehending of the causing and treatment status of AD which can enhance public awareness and tolerance of the disease. In the future, AD research will still face many challenges, but with the continuous exploration of new targets, strategies of treatment, the comprehensive prevention and treatment of AD is still full of hope.

Keywords: Alzheimer's disease, amyloid beta, neuroinflammation, immunotherapy, cognitive intervention

1. Introduction

AD is a brain disease that slowly harm memory, learning, thinking and ability organizations. AD disrupts the transmission of information between nerves, causing many neurons to stop working properly and eventually die, resulting in loss of brain function. At first, AD usually undermines the links between the olfactory cortex and the hippocampus, these are parts of the brain responsible for memory. Then, it continuously influences areas of the cerebral cortex that are involved in language, social interaction, and reasoning. Eventually, neurons in other parts of the brain are affected and slowly lose function. As time goes, people with the disease lose the ability to function independently, and the disease can kill them [1]. About 24 million people worldwide suffer from AD. Especially among the elderly over the age of 65, 1 in 10 people suffer from this disease. Moreover, nearly 1/3 of the elderly over 85 years old suffer from AD [2]. Memory loss is the main

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symptom of AD. These patients may experience symptoms including forgetting conversations or events, having difficulty holding a conversation, getting lost in familiar places and repeating a question or sentence over and over again. They also have difficulty thinking and concentrating. Some people may also develop psychological problems, such as depression, loss of interest in activities, and distrust of others [3].

Amyloid plaques is one of causes of AD. When these proteins become abnormal, they cluster together to form plaques, which can interference the function of neurons [1]. Neurofibrillary tangles are abnormal accumulations of a protein called tau inside neurons. In AD, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming filamentous structures. These structures block the neuron's transport system and can disrupt connections between neurons [1]. Acetylcholine is a neurotransmitter secreted by neurons. The function of this neurotransmitter is transducing signal that has some relationship with memory and learning ability. AD is a neurodegenerative disease, and dysregulation of acetylcholine secretion may also be one of the causes of AD [3].

The FDA approved lecanemab and donanemab, which are immunotherapy drugs that can be used to treat early-stage AD. They target beta-amyloid protein, which helps reduce amyloid plaques in patients' brains [4]. Now adays, acetylcholinesterase (AChE) is the most ordinary therapeutic target worldwide, so, there are many therapies that using AChE as a target. Also, the butyrylcholinesterase (BChE) have the potential to be used to treat AD too [4]. Cognitive stimulation therapy (CST) is also a treatment option. This is a common method used to help people keep their minds active. Cognitive rehabilitation can also help improve symptoms in people with AD. It can help people maintain their thinking skills and achieve their goals. All current treatments cannot accurately treat AD, and scientists have not yet accurately found the exact cause of AD. This article mainly introduces the pathological mechanism of AD, existing drugs, vaccines, etc. and the prospects of AD treatment..

2. Pathological mechanisms of AD

2.1. Amyloid β protein (Aβ)

Aβ is the main component of AD neuritic plaques, and Aβ accumulation is a molecular driver of the pathogenesis and progression of AD. Aβ is generate by division of amyloid precursor protein (APP). Aβ has a dual role, according to two specific processing pathways: the non-amyloidogenic pathway and the amyloidogenic pathway. The yielding and polymerization of Aβ peptides can reduce by the non-amyloidogenic pathway. It has the function of neurons protection, synaptic plasticity promotion and the influences of exerting anti-inflammatory. However, overemphasize on this pathway may break the balance of the metabolism of APP. At the same time, the amyloidogenic pathway produces Aβ40 and Aβ42, these are Aβ peptides. The storing and polymerization of Aβ are tightly related to AD, which can trigger neurodegeneration and produce poisonous substance [5]. Ultimately, dense Aβ aggregation is a hallmark of brain aging and, together with tau neurofibrillary tangles (NTFs), constitutes the pathological hallmark of AD [6].

2.2. Tau protein

Tua mostly inside the human neurons, which exists on the chromosome 17’s long arm at band, which is longer than 100 kb [7]. Tauopathies are caused by the polymerization of tau proteins into neurofibrillary tangles. In the AD patients’ brain, tau is abnormally hyperphosphorylated, which can

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ultimately lead to the disassembly of microtubules and the aggregation of free tau molecules into double helical filaments [8]. Mutations in the microtubule-associated protein tau (MAPT) gene can cause frontotemporal dementia and Parkinson's disease (PiD) associated with chromosome 17 (FTLD-17), demonstrating that tau dysfunction is enough to cause neurodegeneration in the absence of Aβ. AD, PiD and other central nervous system diseases are caused by abnormal accumulation of tau [8].

Tau tangles begin in the brainstem. From there they spread upward to two areas. The first part is the entorhinal cortex, which is the first part of the brain's learning center. There are some damaged brain cells here occur in the early period of AD. Then, the damage spreads to the learning center, the hippocampus, which is a part responsible for memory. The accumulation of tangles in these areas is one of the results of AD that causes memory loss and other symptoms. The amount of unusual tau protein that inside the brain has some relationship with the severity of the stage of the disease. Regularly checking tau protein levels is a reliable predictor and early indicator of cognitive decline [7].

2.3. Neuroinflammation

Systemic inflammation and obesity are also a cause of AD. Obesity makes people more susceptible to viral or bacterial infection, which diametrically increases the feasibility of systemic inflammation. Obesity during midlife has been confirmed as a risk factor for AD. This disease can also cause by other risk factors, such as a high-cholesterol diet, reduced physical activity, and prolonged sitting. At the same time, obesity leads to diminished gut microbial diversity and rise up the levels of pro-inflammatory markers in peripheral blood, so obesity is a factor in AD [9].

Systemic inflammation damages the completeness of the blood-brain barrier (BBB), causing peripheral inflammatory factors to spread to the brain. These factors better induce brain changes and lead to cognitive weaken in AD patients. In addition to the spread of peripheral factors, peripheral inflammation can also be observed inside the brain through the damaged BBB. The transmission of Tau protein. Systemic inflammation also leads to a reduction in the flow of cerebrospinal fluid (CSF) and interstitial fluid (ISF) across the BBB, which also leads to the accumulation of Aβ [10].

2.4. Acetylcholine (ACh)

ACh is a neurotransmitter secreted by neurons and is related to memory and learning. The central cholinergic nervous system can affect the level of ACh by adjusting the composite and secrete of ACh. Basal forebrain cholinergic neurons (BFCN) are important for memory, cognitive and learning functions. They are mainly dependent on nerve growth factor (NGF) and allocate the cortical and hippocampal areas related to memory and learning [11]. There are many nicotinic acetylcholine receptors (NACHR) in the hippocampus, a brain region. AD patients usually have degeneration of cholinergic neurons (BFCN) [11]. The main reason for their degree of dementia and memory loss is the loss of synapses among the basal forebrain and target tissues such as the hippocampus and cortex. Severe neurodegeneration, a decrease in cholinergic neurons and a severe lack of acetylcholine are present in the brain tissue of AD patients [11]. At the same time, the activity of acetylcholine transferase is significantly reduced [11].

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3. Current treatments

3.1. Tau pathology

A small molecule called salsalide nonsteroidal anti-inflammatory drug that has been shown to inhibit tau acetylation62. The study shows in a mouse model of tauopathy, the medicine effectively lowers the t-tau and acetylated ta's scales. This blocked hippocampal shrivel and decreased memory impairment [12]. In tauopathies, O-GlcNAcylation of tau may play a protective role by prophylaxis tau phosphorylation and polymerization. ASN120290 is an O-GlcNAcase (OGA) inhibitor, which is present in cerebrospinal fluid and plasma at similar concentrations, so the resulting complex can easily enter the brain [12]. AD vaccines from other companies and AN-1792 target the natural single copy form of beta-amyloid as a therapeutic target. However, this type of vaccine cannot effectively reduce the symptoms of AD, but it can reduce the amyloid beta plaques in the brain. During the phase II trial, the anti-Aβ antibody bapineuzumab decreased the levels of phosphorylated tau in the cerebrospinal fluid of AD sufferer Because there is no way to effectively relieve AD symptoms, unfortunately, there is no further research on this vaccine [13].

3.2. Therapy targeting A-β

The first inhibitor to enter Phase II clinical trials was LY2886721. It is a BACE1 inhibitor, Aβ need this enzyme for Aβ. However, the drug was stopped in Phase II studies because of four participants had abnormal liver biochemical values [14]. Immunotherapy is considered one of the most favored therapies to amend the AD's progression. AN1792 was the first AD vaccine in these studies [14]. This showed some treatment effects in slowing cognitive decline. The clinical trial was ultimately abrogated because 6% of participants developed aseptic meningoencephalitis. Vanutide cridificar (ACC-001) is a conjugate of multiple short Aβ fragments and does not have the same safety issues as AN1792. The data showed that this vaccine can improve cognitive impairment in AD animal models by generating N-terminal anti-Aβ antibodies. However, the experiment was terminated due to adverse reactions in participants [14]. There are other drugs that have been tested, but for some reason they were discontinued, such as Aducanumab, Gantenerumab, Crenezumab, Solanezumab, Donanemab and Lecanemab. These medicines all ended up testing during phase III [15].

3.3. Current medicines

Tacrine, donepezil, rivastigmine and galantamine are drugs affirmed for the treatment. Donepezil is used to treat patients with severe or advanced AD, and the other drugs are used to treat less severe AD. Still, tacrine has been discontinued in the United States due to its severe hepatotoxicity [14].

The FDA approved two immunotherapy drugs, lecanemab and donanemab, for the treatment of early-stage AD. These drugs target beta-amyloid and help reduce amyloid plaques in the brains of patients, one of the hallmark brain changes. During the 18-month testing phase, the drugs effectively slowed the decrease of cognitive rate in some participants and reduced the level of amyloid in the patients' brains [16]. Possible secondary action of both drugs include brain swelling and bleeding, nausea, fever, chills, body aches, fatigue, low oxygen levels, dizziness, vision changes, seizures and difficulty walking and more [16]. This medication is used to relieve symptoms, allowing few people to have some daily functions longer than they could without the medication. Memantine can assist people with late-stage Alzheimer's keep their ability to do things independently, such as going to the bathroom. Memantine works by regulating glutamate, an important brain chemical. Too much

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glutamate can cause brain cells to die. Headache, diarrhea, dizziness and confusion are earthly side effects [16].

Donepezil, galantamine, and bengalantamine are all cholinesterase inhibitors. These can use for treating AD as well. Donepezil can treat symptoms by stopping the breakdown of acetylcholine in the brain [16]. Galantamine treats less severe symptoms by preventing the breakdown of acetylcholine and stimulating nicotinic receptors in the brain to produce more acetylcholine. Bengalantamine is an advanced version of mild galantamine. It can alleviate some of the side effects of mild galantamine, such as indigestion [16].

Some anti-anxiety medications, for example benzodiazepines, may cause symptoms such as drowsiness, dizziness, falls, and confusion in people with AD. Some antipsychotic drugs used to treat paranoia, hallucinations, delusions, and agitation and aggressive behavior can have serious side effects, such as increasing the risk of death in some people with Alzheimer's. Medicines for treating severe aggression such as Anticonvulsants. Their side effects may cause drowsiness, dizziness, very emotional, and confusion. People with Alzheimer's should not take sleep aids frequently, because they can make people more confused and more likely to fall [16]. However, all of these drugs can only help delay the progression of the symptoms, they cannot completely cure AD. Although there is no drug that can completely cure AD, scientists have been constantly trying to study possible solutions.

3.4. Psychological therapies

Talking therapy is a type of psychological therapies which include cognitive behavioral therapy (CBT), psychodynamic therapy, interpersonal therapy (IPT), family therapy, systemic therapy, and Humanistic therapies. These therapies allow patients to talk about their experiences, mood, ideas, thoughts and feelings. The therapist will determine which type of talking therapy should be used for dependent treatment based on the patient's condition. The reason why talking therapy is effective for AD patients is that they may experience some symptoms of depression and anxiety. Talking therapy provides these patients with an opportunity to express their thoughts and feelings. This can effectively help them reduce negative psychological conditions [17].

4. Conclusion

This article introduces the pathogenesis and principles of AD, including the four major causes of Amyloid β protein, tau protein, Neuroinflammation and Acetylcholine. This article also describes the various existing treatments and how they treat and improve the symptoms of AD, such as Tau pathology, Therapy targeting A-β, Current medicines, and Psychological Therapies. However, there is still no drug or vaccine that can completely cure and prevent AD. This article can help readers better understand the four theories of the pathogenesis of AD and the various medicines and vaccines for AD that have been developed in the past, as well as the reasons why these drugs and vaccines have not been studied further. With the development of science and technology, there is still the possibility of breakthroughs in various aspects of research related to AD. Hope that in the future scientists can develop methods that can completely cure and prevent AD, find the exact cause of AD and reduce the incidence of AD. In the future. there is great hope that the continued research on AD can bring more expect to the patients' families.

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