Research progress on the targets and therapies of Alzheimer's disease

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Abstract. Alzheimer 's disease (AD) is a progressive neurodegenerative disease. Most of the patients have the following characteristics, such as abnormalities in memory, language, and behavioral ability. It is very common in dementia in the elderly. The pathological features are mainly the plaques formed by Aβ protein deposition and the neurofibrillary tangles. The causes of AD are complex, and there are many pathological hypotheses. The current clinical therapeutic drugs for AD are mainly cholinesterase inhibitors developed based on the cholinergic hypothesis and receptor antagonists targeting NMDA receptors. Although there are some research results on the targets based on other hypotheses, further research is needed for clinical application. Nevertheless, in recent years, there have been many new development directions, such as combination therapy. Multi-target combination therapy is expected to achieve better efficacy than traditional single-target therapy. This makes it even more important to develop drugs with different potential targets. This article introduces three current mainstream therapeutic targets and theories, and introduces the drugs based on them. At the same time, we also introduced 3 targets and therapies with good potential in the future, and introduced some current stage results and current drugs based on their research and development.

Keywords: Alzheimer's disease, target, therapy.

1. Introduction

In the early twentieth century, Alzheimer 's disease (AD) was discovered and reported by Alois Alzheimer, a German doctor, for the first time. It is a progressive neurodegenerative disease. The age of the main patients was concentrated in 60 years old and above. According to statistics, there are more than 47 million dementia patients worldwide in 2016, and this figure has exceeded 50 million in 2018 [1]. At the same time, due to the progress of modern medical technology, including public health, living standards, and the progress of citizens ' health ideology, the average life expectancy of human beings around the world has been further extended [2]. The aging of residents in most developed countries is an unchangeable trend. As a disease for the elderly, the impact of Alzheimer 's disease on society has gradually increased with the aging of society. Because Alzheimer 's disease can both physically and psychologically torture patients and make them lose their ability to live. Patients cannot live on their own, and must rely on the help of others. The care for the dementia-type diseases led by AD is very expensive, and there are also high requirements for nursing staff and processes. The World Alzheimer Report (2015) shows that if this trend continues, the whole world will spend nearly $ 2 trillion on dementia care by 2030. If the indirect costs of care are included (such as the resources that the whole society pours into it), this number will be even greater [2]. In general, it is urgent to find a therapy that can greatly solve Alzheimer 's disease in medicine, and it will also provide a great social value.

Alzheimer's disease is a very important disease in senile dementia, and the main clinical manifestations of it are cognitive dysfunction, abnormal daily life behavior, and impaired intelligence [3]. Its pathological features are mainly amyloid plaque deposition and neurofibrillary tangles [4]. Although Alzheimer 's disease has been discovered by humans for more than 100 years, the complete pathogenesis of AD is still unclear. The current research community has created a variety of pathological hypotheses for AD, including the Aβ protein cascade hypothesis, the cholinergic neuron hypothesis, the tau protein hypothesis, the neurovascular hypothesis, etc., and has also achieved some preliminary results. However, the only drugs that are really used in clinical practice are cholinesterase

inhibitors based on the cholinergic hypothesis and receptor antagonists for NMDA receptor targets. Although some therapies based on other hypothesis paths have also been studied, most of them are still in the stage of animal experiments or clinical trials, and there is still a certain distance from large-scale listing to actual treatment. However, it is exciting that combined drug-multi-target (CDMT) may achieve better results in the treatment of AD than single-target therapy. This may open up a new way of thinking for us.

This article summarizes several current mainstream AD therapeutic targets and therapies, and introduces some targets with good potential in the future and examples of their current drug phase results. Based on this, some potential targets and research directions in the future are summarized, and appropriate prospects are made.

2. Current therapies

2.1. Drugs and therapies based on AChE/BuChE targets

In the therapy of AD, the concept of AChE target comes from the cholinergic hypothesis. Researchers have always believed that the pathology of AD has a potential link with the damage to the cholinergic system [5]. The cholinergic neurons in brain are mainly distributed in hippocampus, amygdala, piriform area of limbic system, striatum, basal nucleus of forebrain and so on [6]. The core content of this hypothesis is it holds that in the brains of AD patients, cholinergic nerves have degenerated and cholinesterase activity has increased, resulting in decreased acetylcholine(ACh) levels in certain brain region, such as hippocampus and cortex. This will play a major role in the decline of cognitive ability in AD patients [1]. It has been widely recognized that two different types of cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), are working in human brain. AChE mainly exists in the peripheral region and central nervous system (CNS), while BuChE mainly exists in peripheral region. Both of them can hydrolyze ACh into acetic acid and choline (AchE plays a major role in it) [1]. Ach is a very important neurotransmitter in cholinergic neurons, and participates in many important physiological functions such as memory process, learning process, stress response, sleep, etc. Under the combined action of high activity of cholinesterase and cholinergic neurodegeneration, the level of Ach is significantly low in the AD patients' brain, which leads to the occurrence of this disease. At present, cholinesterase inhibitors targeting AChE are still the main drugs for the treatment of AD.

From a historical point of view, Tacrine is the first clinically used drug designed to treat AD in clinical history, which is a cholinesterase inhibitor. Although it later withdrew from the market due to its strong side effects, it still proves that it is feasible to treat AD by using AChE target. As a second-generation drug after tacrine, rivastigmine (carbamate compound) can selectively inhibit cholinesterase in the brain and hippocampus passing through the blood-brain barrier, and has less inhibition on cholinesterase in other human regions such striatum, pons and heart [3]. However, it still has some side effects, including dizziness, vomiting, headache, diarrhea, etc [7]. Donepezil (a new hexahydro pyridine derivative) is also a second-generation drug just like rivastigmine. Compared with placebo, donepezil can be very effective in restoring the loss of function in AD patients, and the therapeutic effect is not severely affected by the dose [8]. Another drug currently in clinical use is galantamine. It is highly selective for neuronal cholinesterase and can improve cognitive dysfunction in AD patients from mild to moderate. And it was found that galantamine could inhibit the overexpression of β-site app cleaving enzyme 1 in cells, so as to antagonize β-amyloid protein damage, and protect the neurons [3].

Unfortunately, the above several current mainstream drugs can only alleviate the symptoms of AD to a certain extent, they can not completely prevent or prevent the deterioration of the disease. Therefore, based on the idea of inhibiting cholinesterase activity, the development of more effective AD treatment drugs has become a research hotspot. Jaipea et al., tried to achieve the inhibition of cholinesterase by designing piperic amide analogues, and they got quite good results in the experiment.

2.2. Drugs and therapies related to Amyloid-beta protein

Another hypothesis about the pathogeny of Alzheimer's disease is Aβ cascade hypothesis. The specific content of the hypothesis is one possible reason for AD is that the production rate of Amyloid β-protein (Aβ) is much greater than the clearance rate, causing the deposition of Aβ. The mechanism is mainly about the decomposition of amyloid precursor protein (APP). Under the combined action of the β-site APP cleaving enzyme and the γ-site APP cleaving enzyme, the APP will be cleaved into Ab monomer and oligomer, which are biologically toxic. These substances will be deposited outside the cell, thus forming amyloid plaques, accelerating neurofibrillary tangles and triggering a series of neurodegenerative cascades. Finally lead to the death of a large number of neurons and several typical symptoms of AD [1]. There are three main therapeutic strategies targeting Aβ peptides: reduce the formation of Aβ, reduce the Aβ's aggregation and accelerate the degradation of Aβ. Peptide-based inhibitors are used frequently in combating the detrimental effects of Aβ. And they will bind to the Aβ then impede its aggregation and convert toxic Aβ oligomers to non-toxic Aβ fibrils. A pentapeptide sequence KLVFF is considered as a pioneer of designed synthetic peptide-based inhibitors. Peptide KLVFF interacts with Aβ and will prevent the formation of Aβ fibrils [9]. Matsunaga et al. synthesized an octapeptide series from the central hydrophobic core of Aβ, finding that several peptides of them can interfered the interactions of the monomers then inhibit the oligomerization, making those substances become more non-toxic [9]. The representative drug for antagonizing Aβ aggregation is homotaurine. It is a glycosaminoglycan that binds to Aβ monomers. Clinical trials have shown that homotaurine can improve cognitive function in patients with severe AD [6]. Other drugs that antagonize Aβ aggregation include ELND005, melatonin, D737, etc.

2.3. Drugs and therapies targeting NMDA receptor targets

Glutamate is one of the most important neurotransmitters in human body. As a coincidence detector, NMDA receptors can mediate synaptic plasticity. If some synapses have a temporally activation of NMDA receptors, the rapid release of divalent magnesium will let them make plastic changes, which will allow the inflow of divalent calcium cation. And Mg^{2+} is very sensitive, a slight depolarization will let them leave the NMDA channel, causing disorders in memory and learning abilities [10]. Excessive stimulation of glutamate on receptors can lead to neuronal damage, which is a phenomenon called excitatory toxicity. Memantine is an NMDA receptor antagonist. In order to prevent the overstimulation of glutamate, Memantine can specifically bind to the phenyl cyclohexyl piperidine site on the NMDA receptor [3]. Compared with other similar NMDA receptor antagonists, Memantine has fewer side effects but with effective improvement in the behavioral and psychological symptoms of AD patients.

One thing to note is, there are some links between NMDA receptor and the pathological mechanism of Aβ. Theoretically, NMDA receptor probably is a receptor associated with Aβ. The function of NMDA receptor can be heavily influenced by Aβ. In reverse, the activity of NMDA receptors may also affect the formation of Aβ [11].

3. Future therapies

3.1. Tau-targeting therapy

Tau, a kind of microtubule-associated protein mostly found in axons, is functionally a scaffold protein. Tau may form neurofibrillary tangles, and has multiple phosphorylation sites. Microtubules are composed of tubulin and microtubule-associated proteins [12]. The binding ability of phosphorylated tau protein to tubulin will decrease, so that microtubules are no longer stable. In AD patients, tau protein is hyperphosphorylated and aggregates into spiral filaments, which greatly reduces the ability to bind to microtubules, thereby degrading the neuronal skeleton [6].

An emerging therapeutic strategy is to try to reduce the phosphorylation of tau protein. Glycogen synthase kinase 3 (GSK3) is an enzyme that plays a key role in tau phosphorylation. According to

some research, the therapeutic ability of insulin towards AD has been found by some clinical studies, since insulin injection can weaken the activity of GSK3β, thereby reducing the level of tau protein phosphorylation [13].

Another treatment idea is to speed up the degradation of aggregated tau protein, thereby reducing its toxicity. It has been reported found that hsp90, a cellular chaperone, can prevent the degradation of tau protein. Several studies have shown that the aggregation of tau protein can be interfered by Hsp90 inhibitors, and also induce the clearance of aggregates by autophagy [14]. Recently, more researchers in medicinal chemistry domain begin to pay more attention to the design and synthesis of new Hsp90 inhibitors.

3.2. ApoE4-targeting related researches

Apolipoprotein E4 (ApoE4) is an isomer of apolipoprotein E (ApoE). Human's ApoE gene has three polymorphic alleles, encoding ApoE2, ApoE3 and ApoE4 proteins. Among these 3 proteins, the most risky factor would be the ApoE4 [15]. ApoE4 is mainly expressed and synthesized in the liver and brain, and astrocytes is the main production site of ApoE.

The first effect of ApoE4 on AD is that it affects the metabolism of Aβ and aggravates AD. Huynh et al. made an experiment, by reducing the expression of ApoE family proteins in the experimental mice's brain, the occurrence of the Aβ plaques and related neurological adverse reactions can be effectively reduced [16]. And compared to other isomers, ApoE4 has a more obvious effect on promoting the aggregation process of Ab monomer into Ab fiber [17]. As for the mechanism of action, some current studies have shown that ApoE4 preempts the receptors that bind to Aβ, thereby inhibiting the clearance of Aβ [18]. Although the deeper connection between the two is not yet clear, the current known information provides a clue for us to design ApoE4 as a target for the treatment of Aβ oligomers and fibers.

Another effect of ApoE4 on AD is it has some effect on the tau protein. Toledo et al. found that the level of ApoE4 in cerebrospinal fluid of patients was positively correlated with the level of phosphorylated tau protein in cerebrospinal fluid [19]. And related clinical studies have found that patients with ApoEε4 homozygous gene have more severe tau protein pathological tangles and phosphorylation [20]. Current studies have found that ApoE4 can significantly aggravate tau-mediated neurodegenerative diseases, but it is still unknown whether ApoE4 has a deeper mechanism of influence on AD. We need further research on this point.

3.3. Therapeutics for neurovascular injury

Neurovascular unit (NVU) is a complex composed of nerve cells, glial cells (including astrocytes, microglia, oligodendrocytes), vascular cells and extracellular matrix. The various components of NVU cooperate with each other to maintain the physiological balance of brain metabolism and ensure that the physiological function of the brain does not occur abnormal. And the core part of NVU is the blood-brain barrier (BBB). To be more specific about the BBB, it is a highly selective semipermeable membrane between the nervous tissue and the blood. It has the function of physically separating the brain from the blood circulating in the brain [21]. Moreover, BBB can prevent various endogenous or exogenous harmful substances into the brain parenchyma, and can also keep peripheral immune cells out of that region [22]. BBB also play a role in clearing amyloid β-protein. t is generally believed that the dysfunction of pericytes or the instability of blood vessels will cause the BBB to be destroyed, thereby increasing vascular permeability and losing the ability to prevent toxic components and peripheral immune cells from entering the brain parenchyma, and eventually lead to neurodegeneration. In patients with neurodegenerative diseases represented by Alzheimer 's disease, problems such as increased BBB permeability and overall neurovascular dysfunction have been found. Therefore, some studies use NVU damage as an entry point to find new potential therapeutic strategies for AD.

One exciting direction is neural stem cell therapy. It is mainly based on the transplantation of neural stem cells (NSC). Cummings et al. have successfully used neural stem cell therapy in rodents

to improve their AD symptoms [23]. However, there is still a certain distance from the actual clinical application. Some current studies suggest that the current exploration of neural stem cell therapy for AD should focus on the method of sending cells to designated locations and the method of clarifying the source of cells. The current understanding of stem cell therapy is that although it cannot completely treat damaged neurons and NVUs, it can promote the generation of healthy new cell populations to improve neuronal network function.

Another treatment idea is to use statins for treatment. Statins are cholesterol-lowering drugs. Atorvastatin and pitavastatin in statins can affect the biological activity of NVU and also reduce the accumulation of Aβ in the brain. Some recent researchers, Tomoko et al., used the AD model of mice to conduct experiments, and used a number of indicators (such as senile plaques, serum lipid levels, etc.) to determine the therapeutic ability of statins on AD and the protective ability of NVU physiological function. It was clearly found that the two statins in the experiment could effectively improve cognitive ability. And the main path is reducing the level of Aβ in the central nerve system by protecting NVU, so as to achieve the therapeutic effect, which is quite promising.

4. Conclusion

AD is a disease that affects a wide number of people but has extremely complex causes. Unlike other neurological diseases, the difficulty of developing AD drug treatment methods has soared due to the complexity of its causes and the diversity of individual differences. At present, the more mature drugs in clinical application are mainly cholinesterase targets and NMDA receptor targets. Although many potential targets have been found in theory by looking for the pathogenesis of AD, such as tau protein, etc., and some achievements have been made on this basis, there is still a certain distance from the clinical application. After all, further efforts are needed to complete animal experiments and pass clinical tests. Future exploration in the field of AD treatment will first certainly continue to focus on mechanism target exploration and drug development, but researchers are increasingly finding that multi-path synergistic therapeutic effects will be more significant. For example, the combination of memantine and acetylcholinesterase inhibitors has a significantly better effect in the experiment. Therefore, this reminds us to a certain extent that the design of pharmacological drug coupling scheme is also very important. In the future, not only in pathology, further research on the coupling of treatment options may also have surprising results. With the joint efforts of researchers from all walks of life, it is believed that the day when human beings can overcome AD will be getting closer and closer.

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