Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/40/20241239

The study on the preparation of new drugs targeting the pathogenesis and related influencing factors of Alzheimer's disease

Ziyu Zhou

Dalian University of Technology, Dalian, Liaoning, China, 116081

19802466699@163.com

Abstract. With the development of society, Alzheimer's disease has gradually become an important issue in the world health system. However, after a long period of research, the pathogenic factors and mechanisms of Alzheimer's disease are still unclear, which has a serious impact on an increasing number of elderly people. So drug research for Alzheimer's disease is particularly urgent. This article takes Alzheimer's disease as the background, and proposes constructive treatment suggestions and potential targets by studying the impact mechanisms of some substances. The article consists of four parts: Amyloid Precursor Protein, Brain-Gut Axis , the Curcumin, and Glycogen Synthase Kinase 3 Inhibitors. By exploring each mechanism of action, this paper predicts its therapeutic methods and targets in Alzheimer's disease. Through analysis, it is believed that in the future, although people may still not be able to completely cure Alzheimer's disease, we can better transform it into a chronic disease. Updating the original diagnostic methods for blood and cerebrospinal fluid can improve the cure rate and enable early detection and treatment.

Keywords: Alzheimer's disease (AD), Drug, Amyloid Precursor Protein (APP), Gut-Brain Axis, Curcumin, Glycogen Synthase Kinase 3 Inhibitors

1. Introduction

At present, dementia accounts for about 5.3% of elderly people aged 60 and above in China, with Alzheimer's disease being the main type of dementia. Alzheimer's disease has become the fifth leading cause of death among Chinese residents, and its impact on global health is also increasing. The commonly used diagnostic technique now is blood diagnosis. In the past, diagnostic engineers for Alzheimer's disease were based on symptoms, but due to symptoms being the result rather than the cause, diagnostic errors and delays often occurred. The deposition of amyloid protein usually occurs between 5 and 15 years, which means that even if a doctor makes a correct diagnosis, there is no room for treatment if cognitive function has severely declined.

Alzheimer's disease (AD) is a progressive neurodegenerative disease with insidious onset. In clinical practice, comprehensive dementia is characterized by memory impairment, aphasia, loss of recognition, impairment of visual and spatial skills, executive dysfunction, and personality and behavioral changes. The etiology is still unknown. At present, there are very few drugs for treating AD.

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This article briefly describes the mechanisms of factors and substances that can affect the occurrence and development of Alzheimer's disease, and predicts its future development direction.

2. Symptoms and effects of Alzheimer's

September 21st is World Alzheimer's Day. As a neurodegenerative disease with an insidious onset and progressive progression, Alzheimer's disease (AD) is becoming a huge burden on the global public health system. With the increasing trend of the aging population in the world, neurodegenerative diseases are becoming an increasingly serious health problem. According to the latest estimate, by 2050, the global number of dementia patients will reach 152 million, most of whom are caused by Alzheimer's disease. The incidence rate is generally around 3% to 8%, and the specific situation varies from person to person.

The hippocampus is the organ in the human brain that stores short-term memory, and the problem with Alzheimer's disease comes from the hippocampus. Neuropathologically, Alzheimer's disease is characterized by the presence of extracellular deposits of amyloid-β peptides, intracellular neurofibrillary tangles, and atrophy of the basal forebrain cholinergic neurons [1]. Amyloid-β peptides are a raw material for synthesizing proteins, with the main mission of being processed into proteins, but some special substances can flow around in the blood, cerebrospinal fluid, and interstitial fluid. If these substances accumulate in large quantities in the hippocampus, it will cause the neurons in the hippocampus to be unable to breathe and die, resulting in impaired hippocampus function. The thin threads in neuronal cells intertwine counterclockwise to form neuronal fiber tangles. As age increases, the brain begins to age, and the number of nerve fiber tangles suddenly increases, leading to rapid aging of brain function. AD pathology changes majorly involve cholinergic nerve pathways from the frontal base to the cerebral cortex and hippocampus. This is also the main reason why Alzheimer's patients always have cognitive impairment, as these pathways are closely related to human learning and cognition [2].

Alzheimer's disease usually has a hidden onset and continues to progress, mainly manifested as cognitive impairment and non cognitive neuropsychiatric symptoms. The main symptoms include decreased memory, weakened language and thinking abilities, abnormal emotions, strange behaviors, and a loss of work ability. Usually, Alzheimer's disease gradually develops into severe coma or dementia over time. According to research, Alzheimer's patients may die from other diseases on average nine years after clinical diagnosis [3].

It is worth mentioning that by studying families with a genetic predisposition to Alzheimer's disease, all patients underwent tests such as cognitive function assessment, dementia severity, and computed tomography. It was found that all patients and their offspring at different stages of AD had a specific range of atrophy changes in the brain, which worsened as AD symptoms worsened [2]. In addition, microcirculatory disorders are primary and atrophic changes of the temporal lobes are secondary in AD development. Scientists speculate based on the data obtained that AD may start to occur before its symptoms appear, even in childhood, and there is a high possibility of inheritance.

In conclusion, AD has a huge impact on the world's health system, and our top priority now is to research new drugs that can be used to prevent and inhibit the rapid development of AD, and require them to be cheap, free of side effects, and easy to obtain.

3. The mechanism of action of APP and the direction of AD treatment

3.1. Amyloid Precursor Protein

The difference between Alzheimer's disease and other forms of dementia is the pathological reduction of synapses. This is mainly related to tau protein (aggregates of the microtubule-associated hyper-phosphorylated) and the amyloid β peptide (Aβ) .Scientists have discovered from age-related plaques that the amyloid β peptide is a 4.2 kDa peptide (approximately 40 amino acids in length) [1]. It was soon verified that Aβ was developed from a big zprecursor termed as amyloid precursor protein (APP). APP belongs to a large family of proteins with many analogues in mammals, and its structure is

DOI: 10.54254/2753-8818/40/20241239

highly conserved and difficult to change. By alternative splicing, just one APP gene generates several APP species including APP695, APP750, APP751 and so on [1]. They mainly act on the human nervous system and some signal transduction pathways. APP plays an important role in regulating various functions of synapses and human neuromuscular connections. APP is involved in axonal transport through the interaction between its C-terminal intracellular domain (AICD) and Kinesin. Both are closely related to vesicle(a class of molecular ordered assemblies having a closed bilayer structure) transport in synaptic production. In addition, APP also regulates the development of the peripheral nervous system (PNS). This function depends on the NPTY sequence, which is mediated by Numb and Dab to influence the development of mechanosensory organs. AD patients have shown cerebral amyloid angiopathy with deposition of Aβ peptides in the walls of leptomeningeal, cortical arterioles, endothelial cells, smooth muscle cells, adventitial cells, brain pericytes and perivascular cells. Therefore, the elimination of amyloid protein may be the future direction of AD treatment.

3.2. The Brain-Gut Axis

The human gut is home to a large number of microbes and flora, which are intricately linked to the brain through the microbial-gut-brain (MGB) axis. The brain-gut axis means that there is a close connection between the brain and the gut, which can affect each one, such as diarrhea pain and abdominal pain in times of emotional stress. And now scientists have found that constipation or an imbalance in the gut flora can also cause changes in the brain's neurotransmitters and even lead to the possibility of dementia. Studies show that in addition to symptoms such as memory loss and confusion, about 80 percent of patients with classic neurodegenerative diseases such as AD and Parkinson's disease have gastrointestinal symptoms such as nausea and diarrhea. According to research, the increase in this symptom is due to the production of bacteria caused by an imbalance in the gut flora, and this also accelerates the pathogenesis of AD. Additionally, mood disturbances, anxiety, and stress play a role in GI tract disorders such as irritable bowel syndrome, inflammatory bowel disease, and peptic ulceration.

The enteric nervous system (ENS) is composed of a large number of neurons buried in the gastrointestinal wall, which also become the second brain of the human body. AAccordingly, ENS dysfunction may result in central nervous system diseases.Although the ENS system operates independently of the CNS system, MGB continues to mediate between them. MBG is a complex interaction between gut microbiota, neuroendocrine system, nervous system, and ENS. Various stimuli are transmitted from the intestine to the brain, causing corresponding symptoms. This also indicates that some neurological diseases can be treated by adjusting the gut microbiota, such as through the timely and appropriate supplementation of probiotics. So far, the method of fecal microbiota transplantation (FMT) is commonly referred to as bacterial therapy, which can improve neurological diseases caused by MGB axis dysfunction. Research has shown that FMT has a good therapeutic effect on AD, increasing the Firmicutes in AD patients and restoring a relative dynamic balance between gut bacteria and human health. In the future, if a special drug targeting Firmicutes bacteria can be developed to break away from FMT treatment, it can greatly save the cost of AD treatment and reduce the burden on patients [4].

According to research, AD patients exhibit better levels of immune mediated inflammatory cytokines, such as interleukin and some cytokines, compared to non AD patients. This is due to the damage to the intestinal barrier caused by the action of the gut microbiota and the entry of pathogenic bacteria, resulting in intestinal leakage and increased intestinal wall permeability. So the cytokine variations that appear in AD may also serve as potential targets for AD treatment.

In addition, in the use of sterile mouse axon experiments, it was found that the myelin sheath pathway in the prefrontal cortex of AD diseased mice increased, and this characteristic only improved when traditional intestinal bacteria were implanted. An important neural pathway in the MGB axis is composed of a vagus nerve, and pressure suppresses the vagus nerve, causing harmful reactions to the gastrointestinal tract. VNS establishes a connection between the brain and intestines, which is beneficial for monitoring bodily functions and restoring MGB axis balance. ENS mainly relies on

DOI: 10.54254/2753-8818/40/20241239

serotonin to regulate emotions and cognition, playing an important role in AD and MGB. It affects human neurodevelopment and is mainly produced by the intestine, so serotonin is also considered a possible new method for treating AD.

3.3. Curcumin

Curcumin comes from turmeric, a medicinal herb that has the effects of promoting blood circulation, removing blood stasis, and relieving pain. It is the dry rhizome of turmeric, a plant in the ginger family. In the past, curcumin was mainly used to treat inflammation, liver disease, diabetes wounds, and sinusitis. So far, curcumin has been present not only as a drug in human production and life, but also in food and some other products, such as cheese, curryand, and so on. Research has shown that curcumin has multiple phenolic hydroxyl groups, is an insoluble orange yellow powder, and is also one of the few pigments in the plant kingdom with diketones. Spectral evidence shows that curcumin mainly exists in the enol form in both solid and solution forms. Curcumin molecules contain multiple double bonds and active groups such as phenolic hydroxyl and carbonyl groups, thus possessing strong physiological activity. Curcumin has anti-tumor, anti-inflammatory, antioxidant, free radical scavenging, antimicrobial, and other effects, as well as beneficial effects on cardiovascular and digestive systems. It is precisely because of the diversity of its effects that curcumin has become a potential substance for treating Alzheimer's disease and has been extensively studied by scientists in recent years. In addition, curcumin also has a significant impact on the MGB axis mentioned earlier. Curcumin can regulate gut microbiota such as Escherichia coli and Bacteroidetes, restoring the dynamic balance of their MGB axis. A study comparing the populations of the United States and India found that Indians aged 70-79 have a 4.4 times lower incidence of AD compared to Americans of the same age group. Scientists attribute it to the intake of curry and curcumin [5]. The most important influencing factor in studying the relationship between curcumin and AD is the blood-brain barrier(BBB), through which curcumin and other molecules must cross to reach the brain. At present, curcumin has been proven to penetrate BBB due to its hydrophobicity. In addition, it has been proven that curcumin can also interact with A β Combining as an indicator of AD. Curcumin may inhibit the formation of AB plaques, thereby reducing soluble A β level.

Secondly, an experiment on Caenorhabditis elegans found that reducing cholesterol supply can alleviate A β Symptoms caused [5]. This indicates a certain relationship between cholesterol and AD, but its specific mechanism of action is not yet clear. But what can be confirmed is that in some organisms, curcumin can lower cholesterol levels, thereby reducing the process of amyloid protein production in apps. However, whether this method of treating AD can be applied to humans still requires experimental verification.

In known experimental studies, copper ions play a complex role in the pathogenesis of AD. Most scientists believe that copper ions are crucial for AD neurodegeneration, as they may play a role in APP processing and modification. In vivo experiments suggest that an increase in copper ion levels can be associated with A β Direct action, causing A β Permeate at lower pH. In addition to copper ions, changes in calcium signal transduction in AD may also be a cause of memory decline. Because curcumin is a chelating agent for iron and copper ions, curcumin may reduce A β Gather and treat AD. But it is not advisable to increase the intake of curcumin in large quantities, as curcumin can also significantly reduce the concentration of extracellular calcium ions, block signal transduction pathways, and lead to cell death. So, the appropriate intake and reasonable ratio of curcumin, copper ions, zinc ions, and iron ions can become a new direction for treating AD [6].

3.4. Glycogen Synthase Kinase 3 Inhibitors

The pathological diffusion of Tau aggregates in AD usually occurs in a fixed manner along the network of neural anatomical connections. The misfolded Tau protein may promote the misfolding of other monomers in a manner similar to that of prions, leading to the seeding of this misfolded Tau protein, which has a certain degree of transmissibility [7]. After in-depth research on the Tau protein, two kinases responsible for post-translational aberrant modifications were identified, and we

DOI: 10.54254/2753-8818/40/20241239

subsequently identified them as glycogen synthase kinase 3 (GSK-3) and cyclin dependent kinase 5 (CDK-5).

Firstly, regarding glycogen synthase kinase 3 (GSK-3) , it is a highly conserved kinase that is commonly found in mammalian cells. In addition to the earliest discovered regulation of glycogen synthase activity, GSK-3 can also act on numerous signaling proteins and transcription factors, regulating cell differentiation, proliferation, survival, and apoptosis. GSK-3 was first isolated from segmented extracts of rabbit skeletal muscle, and there are mainly two subtypes, GSK-3α and GSK-3β. The two have 98% homology in the catalytic region, with slight differences in the N-terminus and C-terminus. The two have similar structures but different functions, and have a certain degree of tissue specificity. As a serine protein kinase, GSK-3's activity is mainly influenced by its own phosphorylation level α. The main negative feedback regulates insulin mediated glucose homeostasis and glycogen synthesis, while GSK-3 β. It has a related regulatory effect in insulin sensitive tissues. In addition, GSK-3 can also act on numerous signaling proteins and transcription factors, regulating cell responses to WNT (wingless), growth factors, insulin, RTK (Receptor Tyrosine Kinases), and GPCR(Guanosine-binding Protein Coupled Receptor) signals [2]. So currently, in the research of various major diseases such as cancer, neurodegenerative diseases, and neurological and psychiatric disorders, choosing GSK-3 as the treatment target has also received increasing attention. As is well known, GSK-3 plays an important inhibitory role in glucose metabolism, reducing the rate of insulin controlled conversion of glucose to glycogen. Insulin activates protein kinases by binding to receptors, followed by phosphorylation of a serine residue at the N-terminus of GSK-3, leading to functional inactivation. Research data suggests that mild inhibition of GSK-3 may lead to increased insulin sensitivity.

Lithium has always been a weak inhibitor of GSK-3, achieved by inhibiting the PKC signaling pathway. The PKC signaling pathway mainly consists of receptors, G protein coupled receptors, phosphoinositol kinase (PKC), and downstream signaling molecules [8]. The receptors of the PKC signaling pathway are responsible for receiving extracellular signaling molecules, such as hormones, growth factors, etc. The function of G protein coupled receptors is to transmit signals to effectors within cells through G proteins. PKC is a core substance in signaling pathways that can activate or inhibit intracellular target proteins through phosphorylation. Finally, downstream signaling molecules mainly include ion channels, transcription factors, protein kinases, and other substances, responsible for further transmitting signals to various biological processes. The PKC signaling pathway mainly has four functions. It can regulate cell growth, differentiation, and apoptosis by regulating the expression of cell cycle related genes, affecting cell growth rate, promoting cell differentiation in specific directions, and regulating cell life and death. It can also regulate cell migration by affecting the activity of cytoskeletal proteins and regulating the process of cell migration [9]. The PKC signaling pathway is widely involved in various physiological processes in organisms. Under normal physiological conditions, the PKC pathway operates normally and maintains cellular function. However, in the pathological process, the possibility of abnormal activation of the PKC signaling pathway is greatly increased in tumor occurrence and some degenerative diseases (such as AD), leading to cellular dysfunction and affecting body health. Although all of the above indicate that GSK-3 has the potential to serve as a potential target for AD treatment, the main challenge is its specific brain distribution. All drugs need to cross the blood-brain barrier and reach the brain [10]. This means that the ratio of the amount of medication that crosses the blood-brain barrier and enters the brain to the amount taken is crucial. In current research, it is difficult to balance the molecular weight of lipophilic drugs entering the brain with the molecular weight of oral hydrophilic drugs. At the same time, this is also closely related to the patient's own conditions, and the proportion of plasma also affects the treatment effect. If the deviation is too large, the drug will have adverse effects on the body. So, in the future, when studying drugs related to GSK-3 for clinical treatment of AD, an important consideration standard is the one mentioned above.

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4. Conclusion

This paper first introduces the background, causes, and development trends of Alzheimer's disease. Subsequently, four potential substances and methods were proposed as potential targets for AD treatment in the future. The first one is proposed based on the mechanism of action of APP in AD, which also has a positive regulatory effect in AD. The second type is about the recently discussed brain gut axis, where the brain sends signals that cause intestinal peristalsis, digestion and secretion, affect nutrient absorption and distribution, and regulate bacterial balance. The gastrointestinal tract reacts on the brain, affecting nerve transmission signals, causing stress and anxiety in the body, and affecting emotions and behavior. The third and fourth types were proposed based on the effects of curcumin and GKS-3 in AD. These are closely related to the mechanism of action of AD, but a single therapeutic drug for AD has significant drawbacks. How to solve these problems has become a research direction for future AD drugs.

References

[1] Lin, X., & Zhang, Q. (2014). The Drug Development Based on Pathogenetic Research in Alzheimer's. The Drug Development Based on Pathogenetic Research in Alzheimer's Disease, 55.

[2] Leduc, V., Domenger, D., De Beaumont, L., Lalonde, D., Bélanger-Jasmin, S., & Poirier, J. (2011). Function and comorbidities of apolipoprotein e in Alzheimer's disease. International journal of Alzheimer's disease, 2011.

[3] Spalletta, G., De Luca, V., Padovani, A., Rozzini, L., Perri, R., Bruni, A., ... & Orfei, M. (2013). Early onset versus late onset in Alzheimer's disease: What is the reliable cut-off?. Advances in Alzheimer's Disease, 2(01), 40-47.

[4] Patel, M. (2023). The Brain-Gut Axis in Alzheimer's Disease. Advances in Alzheimer's Disease, 12(3), 29-37.

[5] Yao, E. C., & Xue, L. (2014). Therapeutic effects of curcumin on Alzheimer's disease. Advances in Alzheimer's disease, 3(04), 145-159.

[6] Suruchi, U., Sean, J. M., & Aleister, S. (2013). Calcineurin overexpression regulates APP metabolism. Advances in Alzheimer's Disease, 2013.

[7] Martinez, A., Gil, C., & Perez, D. I. (2011). Glycogen synthase kinase 3 inhibitors in the next horizon for Alzheimer's disease treatment. International journal of Alzheimer's disease, 2011.

[8] Maksimovich, I. V. (2012). Certain new aspects of etiology and pathogenesis of Alzheimer's disease. Advances in Alzheimer's Disease, 1(03), 68-76.

[9] Polis, B., & Samson, A. O. (2018). Arginase as a Potential Target in the Treatment of Alzheimer's Disease. Advances in Alzheimer's Disease, 7(04), 119-140.

[10] Srinivasan, V., Kaur, C., Pandi-Perumal, S., Brown, G. M., & Cardinali, D. P. (2011). Melatonin and its agonist ramelteon in Alzheimer's disease: possible therapeutic value. International Journal of Alzheimer's Disease, 2011.