Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220484

Basic Concepts, Hypotheses and Drug Development of Alzheimer's Disease

Jinhe Zhang

Chongqing NO.1 International Study School

zjh0818hh@foxmail.com

Abstract. Alzheimer's disease (AD) is a neurodegenerative disease that involves complicated pathogenesis and etiology that not entirely defined. As the most common form of dementia, AD is irreversibly progressive and aggravates, causing a great burden to global community. Meanwhile, the number of AD patients is growing annually with the global population aging. Unfortunately, there is currently no cure for the disease and the need for effective treatments of AD is urgent. Drug research and development for AD is a long-term and complicated process, which requires a deep understanding of the mechanisms of AD. At present, anti-Tau protein drugs as well as anti-inflammatory drugs are hot research topics. However, the clinical application of drugs still remains to improve various symptoms related to AD. This paper describes the basic concepts of pathology and gives an overview of the pathogenesis theories of AD, which include Aβ hypothesis, Tau protein hyperphosphorylation theory, Cholinergic hypothesis and Inflammatory response. The final onset of AD is jointly caused by multiple mechanisms rather than a single one. In the paper, we summarizes the treatment strategies of AD and explores the status of drug development. This paper will help with understanding the causes of AD and provide insights into drug research and development for AD.

Keywords: Alzheimer's disease, pathogenesis, therapeutic drug.

1. Introduction

Alzheimer's disease (AD) was initially discovered by a German neuropathologist called Alois Alzheimer in 1907. It is a chronic degenerative illness that takes place in the central nervous system and is one of the diseases that cause the most significant threat to human health. According to statistics, there are now more than 50 million AD patients around the globe suffering from this disease. China has over 10 million AD patients, which account for 1/4 of the world's total AD patients, making the country ranking first in the world [1]. Extracellular amyloid-beta (Aβ) protein deposition in the brain of an AD patient is indicative of pathological alterations, followed by the production of senile plaques and the hyperphosphorylation of tau protein, an intracellular microtubule-binding protein, thus resulting in neurofibrillary tangles (NFTs) and neuronal losses [2]. Clinical symptoms of this disease are mainly reflected as cognitive and memory dysfunction, progressive behavioral impairment, and the patient's gradual loss of the ability to self-live. Being progressive and irreversible, AD will cause the death of patients within ten years of diagnosis in normal cases. At present, AD is diagnosed through a combination of neuroimaging examination, cerebrospinal fluid (CSF) examination, peripheral blood antibody examination, and exosome examination. However, there is no practical solution for

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/3/20220484

prevention, early diagnosis, and treatment. Research on AD's pathogenesis is required to prevent and treat AD in the future. In this paper, we focus on the current research on the pathogenesis of AD and the corresponding drug development.

2. Basic concepts

2.1. Aβ protein (amyloid β-protein)

Amyloid precursor protein (APP) produces a polypeptide that contains 39 to 43 amino acids, namely amyloid β-protein (Aβ), under the effect of proteolysis by β- and γ-secretase. Aβ, with a molecular weight of about 4kDa, produces a strong neurotoxic effect upon its accumulation in the cell matrix [3]. It participates in the circulation of blood, cerebrospinal fluid, and interstitial fluid in the human body. Aβ 1~40 and Aβ 1-42 are the most subtypes of Aβ. Some studies have indicated that Aβ 1-42 is more toxic and more prone to aggregation, which eventually forms the core of Aβ precipitation and thus induces neurotoxicity [4].

2.2. Tau protein

Tau protein is a protein related to microtubule (MT), a neuronal cytoskeleton, and is also the most abundant MT-related protein. Tau protein genes are encoded by the gene MAPT, which consists of 16 exons located on the long arm of Chromosome 17 [5, 6]. Typically, tau protein is mainly found in neurons of the central nervous system, partially in oligodendrocytes and astrocytes. Its cellular function is to facilitate the formation of microtubule polymerization through a combination with other tubulins. In the meantime, it can also bind to the formed MT to stabilize MT and reduce the dissociation of other tubulin molecules so that signaling molecules and nutrients can be better transmitted on the MT. Depending on how mRNA exons are spliced, whether exons 2, 3, and 10 are included or not will result in differences in the number of amino-terminal insertions and microtubule-binding repeats in tau protein. There are six isoforms of tau protein, namely 0N3R (a tau isoform with zero amino-terminal insertion but with three microtubule-binding repeats), 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R.

2.3. Neurotransmitters: glutamate and acetylcholine

The neurotransmitter is a type of chemical molecule which is able to transmit signals. It is vital for message transmission between neurons or between neurons and effector cells, such as muscle cells and glands. Both glutamate and acetylcholine are neurotransmitters. As an acidic amino acid, glutamic acid is mainly found in cereal grains and animal brains, with a significant impact on protein metabolism in vivo and glutamatergic neurons which produce the glutamate are neurons that are very important for the central nervous system. Acetylcholine (Ach) is a crucial neurotransmitter in brain neuron axon transmission [7]. Some studies have shown that acetylcholinesterase (AChE) and Choline acetyltransferase (ChAT) play significant roles in human memory and learning [8]. AD patients have defects in the functions of his central cholinergic nervous system, such as the generation and release of acetylcholine and AChE. Also, previous studies have demonstrated that the cause of early memory dysfunction in AD patients may be associated with the interaction between AChE and Aβ fibrils, which potentially affect the generation of Aβ fibrils [9].

2.4. Microglia and astrocytes

As a defense mechanism and the resident microphage for the central nervous system (CNS), microglia have a share of 5% to 10% among all glial cells in the CNS. The function of microglia involves potential risk factors for cell injury or microcirculation disturbances caused by the generation of inflammatory cytokines induced by bacteria or pathogens [10, 11]. Some studies have shown that activated microglia are mainly found near Aβ senile plaques in the brain tissues of AD animals [12]. The relationship between Aβ protein fibrils and activated microglia requires further exploration. Astrocytes are specialized glial cells that come from the neuroepithelium. Astrocytes are also the

DOI: 10.54254/2753-8818/3/20220484

largest and most widely distributed glial cells in the human body. Their main function is to support or separate nerve cells and regulate neurotransmitters. Meanwhile, astrocytes are also closely correlated with blood-brain barriers, therefore controlling the space capacity outside cells, taking up nutrients from the blood, and supplying these nutrients to neurons [13-15]. Studies have shown that the increased expression of nitric oxide synthase (Nos22) is closely related to the activation of astrocytes [16]. After astrocytes are activated, a large number of inflammatory factors will be released by the reactive astrocytes, thereby inducing neuroinflammation [17]. Early studies on the astrocytes-related neuroimmune mechanism of AD have proposed the signal transmission between glial cells and neurons could be interrupted due to the abnormality of astrocyte morphology and functions, eventually causing neurodegenerative diseases [18]. Additionally, there may be a direct connection between astrocytes and Aβ protein, especially in the production and clearance of the Aβ [15].

3. Related hypotheses

3.1. Aβ hypothesis

The Aβhypothesis is mainly described as follows: Under the continuous hydrolysis of APP, it produces Aβ peptides, which then precipitate and aggregate in the extracellular matrix. Soluble Aβ aggregates are considered to be responsible for neurotoxicity, which may lead to cognitive impairment in patients [19-21]. Additionally, the Aβ hypothesis suggests that the interaction between Aβ and amyloid precursors can affect the pathological process of AD [22]. Meanwhile, the deposition of extracellular Aβ will also induce the formation of senile plaques, which will affect the functions of neurons, microglia, and astrocytes and result in neurotoxicity and the inflammatory response of the neural system [23, 24]. Protein plaques are the leading cause of synaptic dysfunction, neuronal damage death and induce AD formation together with other factors such as tau protein.

3.2. Tau protein hyperphosphorylation theory

Normally, tau protein predominantly localizes to neuronal axons of the central nervous system. After binding to tubulin, tau protein maintains the stability of microtubules [25]. In an average adult human brain, the tau protein contains approximately 2 to 3 phosphate groups; while in the brain of an AD patient, the tau protein contains 5 to 9 ones. This is well known as the hyperphosphorylation of tau protein. The hyperphosphorylated tau protein will disassociate from the microtubule and form a paired helical aggregation structure with other tau protein molecules. Usually, the hyperphosphorylation of tau protein starts from the intima cortex of the brain and then gradually expands to multiple regions such as the hippocampus, etc. The hyperphosphorylation of one tau protein will accelerate the phosphorylation of other tau proteins. Hyperphosphorylated tau protein can spread from neurons to others through neuronal synapses, and hyperphosphorylation of tau protein will disrupt neuronal synapses, resulting in synaptic losses and neuronal cell death [26, 27]. In the brain of AD patients, the disassociation of hyperphosphorylated tau protein destabilizes the microtubules and causes the loss of functions of microtubules. This will lead to the loss of functions of the neuronal and synaptic proteins eventually and the formation of neurofibrillary tangles (NFTs) [28].

3.3. Cholinergic hypothesis

As stated in the cholinergic hypothesis, the activity of acetylcholinesterase and acetylcholine transferase decreases due to the decrease in the density of cholinergic receptors, such as muscarinic receptors (M-type receptors), thus leading to the further reduction of acetylcholine concentration. Reduced levels of acetylcholine may cause dysfunction of cholinergic neurons and even of brain tissues. Studies have shown an important relationship between the cholinergic system and the formation of memory [29]. In the case of low cholinergic activity in the brain of AD patients, the cholinergic neurons are prominently reduced. In addition, cholinergic receptors may reduce the generation of Aβ aggregates and the hyperphosphorylation of tau protein with the aid of agonists [21, 30].

DOI: 10.54254/2753-8818/3/20220484

3.4. Inflammatory response

An inflammatory response is a protective response of the CNS. However, if it's excessively intense, it can cause damage to the nerve system. The inflammatory response is always active during the development of AD's pathological process. Inflammatory factors are excessively released from glial cells in the CNS due to the activation of Aβ as an immunogen. Studies have demonstrated that Aβ can behave as an inducing factor of the immune inflammation response, which plays a vital role in the cascade reaction of AD [23, 24, 31]. Due to its ability to release anti-inflammatory and pro-inflammatory factors, microglia can introduce the inflammatory response by the binding of Aβ protein aggregates to the receptors on its surface, such as scavenger receptor 1 (SCARAl), B class scavenger receptor 36 (CD36), etc., [32, 33]. Additionally, Aβ fibrils can induce the release of reactive oxygen species (ROS) by activating the oxidation of the reduced Nicotinamide adenine dinucleotide phosphate (NADPH), which eventually produces neurotoxins [10, 34], though microglia will partially mitigate the damage of neurotoxin by inhibiting the secretion of inflammatory cytokines.

4. Drug delelopment

4.1. Clinical drugs for AD

4.1.1. NMDA receptor antagonists. The N-methyl-D-aspartic acid receptor (NMDA) is a subtype of glutamate receptor. With a complex molecular structure, it is vital for the development of the nervous system. For instance, it can regulate neuronal survival and participate in the formation of synapses. AD patients show obvious symptoms of neurodegenerative dementia when the function of their glutamatergic receptor (especially the NMDA receptor) is impaired. Glutamate neurons play an essential role in the cognitive regulation, memory, and learning of humans [35, 36]. As the first NMDA receptor antagonist for treating moderate-to-severe ADs, memantine is a voltage-dependent, noncompetitive NMDA receptor antagonist with moderate affinity. It can be used to block neuronal damage caused by elevated glutamate concentration without affecting the physiological activity of NMDA receptors.

4.1.2. Cholinesterase inhibitors (ChEIs). According to the cholinergic hypothesis, cholinesterase inhibitory drugs are effective in the treatment of mild-to-moderate ADs. By reducing the degradation of acetylcholine, inhibiting the activity of acetylcholinesterase, and increasing the concentration of acetylcholine between the synapses, cholinesterase inhibitors are effective in improving the cognitive functions of AD patients. Tacrine [37], Donepezil [38], Rivastigmine [39], and Galanthamine [40] are typically representative of cholinesterase inhibitors. However, the side effects of some cholinesterase inhibitors are significant, such as the severe hepatotoxicity of Tacrine [41]. Donepezil and Galanthamine, with relatively fewer side effects, are more widely used in the clinical treatment of AD, but Donepezil is less effective in improving the symptoms of AD patients.

4.2. Potential drugs for AD

4.1.3. Anti-Aβ drugs. Anti- Aβ drugs produce a significant therapeutic effect on mild AD. According to the Aβ hypothesis, which is the central AD pathogenesis hypothesis, the drug development is to prevent the generation of Aβ or facilitate its degradation. Some studies have pointed out that AZD3293, a β-secretase inhibitor, can promote the degradation of Aβ through immunity to inflammatory response, meanwhile γ-secretase and β-secretase are crucial for Aβ formation [42]. Aducanumab, a monoclonal antibody drug jointly developed by Biogen and Eisai companies, is highly effective for the treatment of AD. It can significantly reduce the amount of Aβ in the brain of patients, improve the patients' cognitive ability and hopefully treat AD [43, 44].

DOI: 10.54254/2753-8818/3/20220484

4.1.4. Anti-tau protein drugs. Hyperphosphorylation of Tau protein is one of the main pathogenic mechanisms for AD. The tau-targeted research plays an essential role in AD research. Currently, there is no tau-targeted drug in the market and the development of the drug is still at the early stage. However, most of the tau-related inhibitors, such as Semorine-mab, Gosuranemab, and Zagotenemab, are undergoing the phase II clinical stage and their follow-up research is to be further developed. The therapy strategy mainly focuses on the inhibition of tau protein aggregation, the inhibition of tau protein hyperphosphorylation, and the degradation of tau protein[45].

4.1.5. Anti-inflammatory drugs. An inflammatory response always accompanies the incidence and development of AD. The excessive activation of microglia caused by the accumulation of Aβ aggregates in the brain leads to the release of pro-inflammatory factors, which play an important role in AD development. As a potential target for the treatment of AD, the inflammatory response has no targeting drug yet. Most of the anti-inflammatory drugs on the market, such as Diclofenac Sodium, Rofecoxib, and Nimesulide, have some effect on the relief of cognitive impairment caused by AD. Considering inflammatory response, blocking the inflammatory pathway of microglia may be a new direction to develop anti-inflammatory drugs for AD. Few studies have been conducted on the treatment of AD with anti-inflammatory medications and comprehensive research is needed [46].

5. Summary

As a chronic degenerative disease in the nervous system, which involves complex pathogenesis and many hypotheses, AD is undoubtedly a complicated disease. Its final onset is jointly caused by multiple mechanisms rather than a single one. The research on the treatment of AD is a massive challenge for the current medical technology. However, with the development and improvement of medicine, biology, and technology, more breakthroughs will happen in the research of AD treatment and related drugs.

References

[1] Chan, et al., Epidemiology of Alzheimers disease and other forms of dementia in China, 1990–2010: a systematic review and analysis. Lancet London, 2013.
[2] Mittal, G., et al., Development and evaluation of polymer nanoparticles for oral delivery of estradiol to rat brain in a model of Alzheimer's pathology. Journal of Controlled Release, 2010. 150(2): p. 220-228.
[3] Selkoe, D.J., Alzheimer's Disease: Genes, Proteins, and Therapy. Physiological Reviews, 2001. 81(2): p. 741-766.
[4] Burdick, D., et al., Assembly and aggregation properties of synthetic Alzheimer's A4/beta amyloid peptide analogs. J.biol.chem, 1992. 267(1): p. 546.
[5] Andreadis, A., Misregulation of Tau Alternative Splicing in Neurodegeneration and Dementia. Progress in Molecular & Subcellular Biology, 2006. 44(1): p. 89.
[6] Wang, Y. and E. Mandelkow, Tau in physiology and pathology. Nature Reviews Neuroence, 2016. 17(1): p. 5-21.
[7] Carageorgiou, H., et al., Changes in acetylcholinesterase, Na+,K+-ATPase, and Mg2+-ATPase activities in the frontal cortex and the hippocampus of hyper- and hypothyroid adult rats. Metabolism-clinical & Experimental, 2007. 56(8): p. 1104-1110.
[8] Gold, P.E., Acetylcholine modulation of neural systems involved in learning and memory. Neurobiology of Learning & Memory, 2003. 80(3): p. 194-210.
[9] Atsushi and Sasaki, Microglia and brain macrophages: An update. Neuropathology, 2017.
[10] Calsolaro, V. and P. Edison, Neuroinflammation in Alzheimer's disease: Current evidence and futuredirections. Alzheimer's & Dementia, 2016. 12(6).
[11] Yuan, R., R. Sun, and X. Liu, Caspase-1 activation contributes to Nod2-induced tolerance in microglia cells. Journal of Shandong University (Health Science), 2015. 53: p. 6.
[12] Hemonnot, A.L., et al., Microglia in Alzheimer Disease: Well-Known Targets and New

DOI: 10.54254/2753-8818/3/20220484

Opportunities. Frontiers in Aging Neuroscience, 2019. 11: p. 233.
[13] Alexei, et al., Physiology of Astroglia. Advances in experimental medicine and biology, 2019. 1175: p. 45-91.
[14] Ferrer and Isidro, Diversity of astroglial responses across human neurodegenerative disorders and brain aging. Brain Pathology, 2017. 27(5): p. 645.
[15] Arranz, A.M. and B. De Strooper, The role of astroglia in Alzheimer's disease: pathophysiology and clinical implications. The Lancet Neurology, 2019.
[16] Wang, P. and Y. Ye, Filamentous recombinant human Tau activates primary astrocytes via an integrin receptor complex. Nature Communications, 2021.
[17] Lambertsen, K., B. Finsen, and B. Clausen, Post-stroke inflammation-target or tool for therapy? Acta Neuropathologica, 2018: p. 15.
[18] Benveniste, E.N., L.P. Tang, and R.M. Law, Differential regulation of astrocyte TNF-alpha expression by the cytokines TGF-beta, IL-6 and IL-10. International Journal of Developmental Neuroscience the Official Journal of the International Society for Developmental Neuroscience, 1995. 13(3-4): p. 341.
[19] Cleary, J.P., et al., Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. Nature Neuroscience, 2005. 8(1): p. 79-84.
[20] Grutzendler, J., et al., Various Dendritic Abnormalities Are Associated with Fibrillar Amyloid Deposits in Alzheimer's Disease. Annals of the New York Academy of Sciences, 2010. 1097(1): p. 30-39.
[21] Tsai, J., et al., Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nature Neuroscience, 2004. 7(11): p. 1181-1183.
[22] Verma, S., et al., Alzheimer's disease like pathology induced six weeks after aggregated amyloid-beta injection in rats: increased oxidative stress and impaired long-term memory with anxiety-like behavior. Neurological Research An Interdisciplinary Quarterly Journal, 2016. 38: p. 9.
[23] Porrini, V., et al., CHF5074 (CSP-1103) induces microglia alternative activation in plaque-free Tg2576 mice and primary glial cultures exposed to beta-amyloid. Neuroscience, 2015. 302: p. 112-120.
[24] Lian, H., et al., Astrocyte-Microglia Cross Talk through Complement Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer's Disease. Journal of Neuroscience, 2016. 36(2): p. 577-589.
[25] Guo, T., W. Noble, and D.P. Hanger, Roles of tau protein in health and disease. Acta Neuropathologica, 2017. 133(5): p. 1-40.
[26] Si, Z., et al., Heme Oxygenase 1 Induces Tau Oligomer Formation and Synapse Aberrations in Hippocampal Neurons. Journal of Alzheimer's disease: JAD, 2018. 65: p. 1-11.
[27] Wagner, J., et al., Reducing tau aggregates with anle138b delays disease progression in a mouse model of tauopathies. Acta Neuropathologica, 2015. 130(5): p. 619-631.
[28] Xu, J., et al., The Role of the Tau Protein in Alzheimer's Disease. Progress in Modern Biomedicine, 2015. 15(3): p. 3.
[29] Zheng, H., M.B.H. Youdim, and M. Fridkin, Selective Acetylcholinesterase Inhibitor Activated by Acetylcholinesterase Releases an Active Chelator with Neurorescuing and Anti-Amyloid Activities. Acs Chemical Neuroscience, 2010. 1(11): p. 737-46.
[30] Kong, X., W. Yu, and Z. Guan, The activation of astrocytic α7 nicotinic receptor inhibit β-amyloid aggregation. Chinese Journal of Geronotology, 2016. 36(13): p. 3112-3115.
[31] Fuller, S., M. Steele, and G. Münch, Activated astroglia during chronic inflammation in Alzheimer's disease--do they neglect their neurosupportive roles? Mutation Research/fundamental & Molecular Mechanisms of Mutagenesis, 2010. 690(1-2): p. 40-49.
[32] Claudia, F.P., et al., Is Alzheimer's disease an inflammasomopathy? Ageing Research Reviews, 2019. 56.
[33] Heneka, M.T., et al., Neuroinflammation in Alzheimer's disease. The Lancet Neurology, 2015.

DOI: 10.54254/2753-8818/3/20220484

[34] Schilling, T. and C. Eder, Amyloid-β-induced reactive oxygen species production and priming are differentially regulated by ion channels in microglia. Journal of Cellular Physiology, 2011. 226(12): p. 3295-3302.
[35] Brown, T., et al., Long-term synaptic potentiation. Science, 1988. 242(4879): p. 724-728.
[36] Reiner, A. and J. Levitz, review glutamatergic signaling in the central nervous system: ionotropic and metabotropic receptors in concert. 2019.
[37] Cristóbal, D. and J. Marco-Contelles, Tacrines for Alzheimer's disease therapy. III. The PyridoTacrines. European Journal of Medicinal Chemistry, 2019. 166: p. 381-389.
[38] Sugimoto, H., et al., Donepezil Hydrochloride (E2020) and Other Acetylcholinesterase Inhibitors. Current Medicinal Chemistry, 2000. 7(3): p. -.
[39] Seltzer, B., Galantamine-ER for the treatment of mild-to-moderate Alzheimer's disease. Clinical Interventions in Aging, 2010. 5(1): p. 1-6.
[40] Birks, J., et al., Rivastigmine for Alzheimer's disease. Cochrane Database of Systematic Reviews, 2009. 38(2): p. 15.
[41] Nakagawa, R., et al., Long-term effect of galantamine on cognitive function in patients with Alzheimer's disease versus a simulated disease trajectory: an observational study in the clinical setting. Neuropsychiatr Dis Treat, 2017. 13: p. 1115-1124.
[42] Bai, J., et al., Establishment of Affinity and Bioactivity Analysis Methods for Monoclonal Antibody Targeting Aβ and AL. Chinese Journal of Pharmaceuticals, 2019. 50(11): p. 1290-1295.
[43] Schneider, L., A resurrection of aducanumab for Alzheimer's disease. The Lancet Neurology, 2020. 19(2): p. 111-112.
[44] Sevigny, J., et al., The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature, 2016. 537(7618): p. 50.
[45] Wolfe, M.S., Targets and Strategies Toward the Development of Alzheimer Therapeutics. Springer International Publishing, 2016: p. 1-25.
[46] Teng, Y., et al., Process in Alzheimer’s Disease Drug Development Journal of Tianjin University of Science & Technolog, 2022. 37(1): p. 10.