Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/75/2024.LA19356

Advances in the principles and treatment of Alzheimer's disease

Yuxuan Zhuang

International Department of Quanzhou No. 5 Middle School, Fujian Province, China

u3641828@connect.hku.hk

Abstract. Alzheimer disease (AD) has become a heat topic since the number of populations suffering from AD is continuously ascending, causing burdens for the whole society [1]. AD is caused by the presence of β-amyloid-containing plaques and tau-containing neurofibrillary tangles [2]. Therapeutic endeavors are still struggling to find targets based on this mechanism. While achieving therapeutic treatments which slower the process of AD cognitive impairment, treatment that can completely cure AD has not been developed. This Primer explains the mechanism of AD from the prospective of synaptic disorder which mainly results from the aggregation of Aβplaques and tau protein which both prevent neuronal signaling. In addition, this Primer emphasize advances in its diagnosis, including clinical diagnosis and advances in biomarkers, as well as the side effect of previous diagnosis and relevant hypothesis of improvement.

Keywords: AD, Epidemiology, Treatment.

1. Introduction

As the aging society arriving, Alzheimer's disease (AD) has brought heavy mental, psychological and socioeconomic burdens to the global public health. It is defined as a neurodegenerative disorder characterized by β-amyloid (Aβ)-containing extracellular plaques and tau-containing intracellular neurofibrillary tangles.

The severity of cognitive impairment can be categorized into stages. The earliest manifestations can be a subjective decline in mental abilities, specifically in the absence of impaired performance on objective cognitive testing. Mild cognitive impairment (MCI) for AD is defined as the earliest symptomatic stage of cognitive impairment in which a single cognitive domain or, possibly, multiple cognitive domains are impaired to an extent of at least a mild whilst most of the function are preserved [3]. EEG showed background EEG as a slow rhythm, and CT showed normal or ventricular enlargement and widened sulci. By contrast, dementia refers to cognitive impairment to an extent that affect independence as well as everyday life. The EEG shows diffuse slow waves and CT shows ventricular enlargement and sulcus widening [4].

Originally, AD was regarded as a clinicopathological entity, which means that, if the patient fulfilled the clinical syndrome of dementia and other conditions were ruled out, one could give AD pathology as the conclusion. Currently, with the improvement of clinical sophistication as well as biomarkers of AD, namely cerebrospinal fluid (CSF) and PET markers for Aβ and tau, has totally changed the concept of AD from a clinicopathological entity to a neurobiological condition that affects cognition [5].

© 2025 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: 10.54254/2753-8818/75/2024.LA19356

Specifically, according to the ATN [amyloid (A) / pathological tau (T) / neurodegeneration or neuronal damage (N)] diagnostic framework, PET or CSF test indicates positive A βin the brain, which can be included in the AD disease spectrum (Alzheimer's continuum) regardless of normal cognitive function, mild impairment, or dementia. Expert believes that for AD patients who cannot be confirmed by pathological and biological markers, conform to the clinical characteristics of neuropsychological cognitive impairment and head MRI structural imaging features, and exclude other types of MCI, such as Parkinson's disease, vascular disease, Lewy disease, can be clinically diagnosed as ''very likely AD''

This Primer reviews the epidemiology and risk factors of the cognitive manifestations of AD and summarizes the pathophysiology of this disorder. In addition, this Primer highlights advances in its diagnosis, including clinical diagnosis and advances in biomarkers, as well as the side effect of previous diagnosis and relevant hypothesis of improvement.

2. Epidemiology

2.1. Incidence and prevalence

Due to the lack of complete survey data on the prevalence of Alzheimer's disease and other dementia, evidence-based research methods are used to search the epidemiological survey literature of Alzheimer's disease published from 1985 to 2019, involving the usage of meta-analysis to calculate the combined prevalence of AD included in the study, and calculate the prevalence of Alzheimer's disease and other dementia in all age groups [6]. For China, in 2022, the elderly population over 60 years old is 28004 million based by the composition of 2020. The composition ratio of each age group over 60 and population of each age in 2022 is calculated, and the estimate of patients of each age group is calculated according to the prevalence rate. The prevalence was 2.4% (95% Cl, 2.0-2.7) in men and 4.2% (95% Cl 3.6 to 4.7) in women. Studies have shown that: In China, among people aged 60 years old and above, the prevalence of dementia is 6.04%, among which Alzheimer's disease is 3.94%, vascular dementia is 1.57%, and other types of dementia is 0.53% [7].

2.2. Risk factors

Age is the most important risk factor for both dementia and AD. Lifestyle is also a factor. In midlife, several modifiable risk factors which associate with an increased risk of 1.5 to 1.8 in later-life dementia may occur, in particular metabolic factors including hypertension, obesity and low HDL cholesterol and traumatic brain injury and alcohol abuse [8]. In later life, smoking, depression, low physical activity, social isolation, diabetes mellitus and air pollution are risk factors of similar magnitude for dementia [9].

3. Pathophysiology

3.1. The amyloid-like protein hypothesis

APP is a single trans-membrane protein that is enriched in neuronal synapses, which is cleavage by α-secretase in most situations, generating APPsα and αCTF.αCTF is subsequently cleaved by γ-secretase into p3 and AICD.This clearing process generates soluble products that cause no harm to human body. However, the critical molecule causing Alzheimer disease, Aβ peptides are derived from APP following the cleavage of APP by β-secretases and γ-secretases (known as the amyloidogenic pathway). The most abundant species of Aβ are 27–43 amino acids in length[10]. After production, Aβ is secreted into the extracellular space as a monomer. *It is noticeable that* Aβis the part of APP that enriched inside the membrane of neuronal synapses, where is hydrophobic, leading to the hydrophobic property of Aβ. Thus, when Aβ is secreted into the hydrophilic extracellular space, it has a high propensity to aggregate, forming Aβ-containing extracellular neurotic plaques, which are found to be deposited preventing functional connectivity between brain regions.

DOI: 10.54254/2753-8818/75/2024.LA19356

3.2. The hyperphosphorylation hypothesis of tau protein

Tau is a microtubule-associated protein. Normally, it is present in the cytoplasm of axons but sometimes is also present in presynaptic and postsynaptic compartments which associate with the nuclear membrane. The main function of tau is microtubule stabilization [11]. Aβ-containing extracellular neurotic plaques initiates pathways inside the neuron that leads to activation of kinase ,an enzyme that transfer phosphate groups to the Tau protein The tau protein then changed a shape, stop supporting the microtubules, causing microtubules to stop functioning.Tau proteins that are free in the cytoplasm interact and polymerize forming insoluble straight filaments and double-stranded helical filaments, which eventually lead to NFTs ,which reduces the number of synapses and produce neurotoxicity. Soluble tau may be more toxic than NFTs, which not only leads to the spread of pathological tau, but also affects cognitive function.

4. Therapy

4.1. Current status of non-pharmacologic treatments

Non-pharmacologic treatments (NPT) are considered as a safe treatment option with fewer side effects. NPT involves various disciplines, each trying to positively influence the cognitive, emotional and other behavioral and psychological symptoms of AD. This paper presents three non-pharmacologic treatment methods.

4.1.1. Stay away from loneliness therapy. Loneliness is a subjective feeling that stems from perceived differences between expectations and actual social relationships. Reports show a significant relationship between loneliness and AD, with an excessive "risk" of AD ranging from 15% to 64% compared to non-loners. This idea is further supported by experimental data on cross-sectional loneliness associated with higher brain A β load in studies using positron emission tomography imaging, especially in APOE 4 carriers, and with greater tau pathology, suggesting that loneliness may be a sensitive clinical marker for pathological brain changes in AD in older adults.

4.1.2. Aromatherapy. Aromatherapy is part of the phytotherapy discipline. The principle is to have the whole plant or part of the plant for medicinal use, and the use of pure essential oil from aromatic plants through transdermal administration or inhalation and absorption of essential oil can activate the autonomic nervous system, induce the response of the limbic system and hypothalamus. Rage, lavender, and rosemary have shown anxiolytic, anti-inflammatory, antioxidant, and neuroprotective effects. They also show therapeutic potential for common neurological disorders, including AD, Parkinson's disease, migraine, and cognitive impairment. In biochemical experiments, A β protein and phospho-tau levels were significantly reduced in both the hippocampus and olfactory bulb of aromatic-treated mice [12]. The rule recommends the use of an incense pendant during the day so that the fragrance of the essential oil reaches the user even if the user moves, and use a common diffuser in the bedroom at night.

4.1.3. Acupuncture therapy. Acupuncture therapy is a traditional Chinese non-pharmacological treatment in TCM and can be used as an adjuvant treatment option for AD to avoid possible side effects from pharmacological use. It has been shown that the model rat with severely impaired nerve function clearly regulated axin and β -catenin expression in the rat hippocampus by electroacupuncture and moxibustion pretreatment. Acupuncture influences on AD through various mechanisms, including increased brain energy metabolism, decreased protein A β deposition, increased pro-survival proteins, decreased apoptotic proteins, activated antioxidant function, suppressed neuroinflammation, and increased neurogenesis. The five acupoints of Baihui (GV 20), Daishen (GV 14), Fengfeng (GV 16), Dummen (GV 15) and atrium (GV 24) may have a good therapeutic effect on the treatment of AD [13].

DOI: 10.54254/2753-8818/75/2024.LA19356

4.2. Drug therapy

There are two types of common drugs: ones called acetylcholinesterase inhibitors, including donepezil, carbabortin, and galantamine; and those called N-methyl-D-aspartate (NMDA) receptor antagonists, including memantine [14]. They are the most mature and most developed drugs as for now, but we found that it could not focus on the root cause of the disease. Meanwhile, In the early stage of the disease can improve some symptoms of the patient, but cannot prevent the progress of the disease, the effective time after long-term use is shortened, and there are greater side effects on some patients. For the drugs that tag to the root cause, beta amyloid protein based monoclonal antibody like Lecanemad and Tau based chemical drug like MTC each has their own demerits. Lecanemab may cause cerebral hemorrhage and MTC may cause you to have gastrointestinal and urinary adverse events [15].

4.2.1. N-methyl-D-aspartate receptor antagonists. One of the receptors of glutamate acting as a neurotransmitter in the central nervous system is the NMDA receptor. In the central nervous system, high levels of glutamate (Glu) can lead to excessive excitation of their corresponding NMDA receptors, which can lead to neurotoxic effects that induce and aggravate Alzheimer's disease. So, if we use drugs to block NMDA receptors, we can reduce the efficacy of glutamate, thus reducing the neurotoxic effects of excess glutamate, and thus treat Alzheimer's disease [16].

4.2.2. Lecanemab. Lencainizumab (Lecanemab) is a humanized monoclonal antibody used for the treatment of Alzheimer's disease that selectively neutralizes and removes soluble and toxic β -amyloid protein (A β) aggregates that cause Alzheimer's disease neuropathy. lecanemab Targeting amyloid forms that have not yet been clustered together, including oligomers, protofibril, fibril, and amyloid aggregates, among others. And thus, fundamentally treat AD [17].

4.2.3. MTC. It is demonstrated that MT, namely methylthionium plays an effective role in reducing the form of tau protein. MTC and LMT are different states of the drug, but it is MT which works. Besides, LMT, as the reduced form of methylthionium did the trick more significantly. The role of MT is, because Tau four repeat isomer and three repeat isomers (the formation of intermolecular disulfide bonds) will promote tau aggregation [11], and MT can be used as a reducing agent oxidation reaction, the cysteine residue modification to sulphonic acid, and the sulfonic acid can four repeat, three repeat Tau into not aggregate mono state, so as to prevent the formation of filament and toxic precursor, to inhibit the aggregation of tau [18].

4.3. Other treatments

4.3.1. Transcranial Magnetic Stimulation. As a non-invasive brain stimulation regimen, repetitive Transcranial Magnetic Stimulation (rTMS) alleviates symptoms associated with cognitive impairment in mild-to-moderate AD patients. Its mechanism of action, reduce β -amyloid generation, and improve the efficiency of brain excretion pathway clearance, thus significantly reduce the brain β -amyloid deposition, inhibit the excessive activation of microglia and astrocytes, and improve the prefrontal cortex and hippocampus memory related brain areas of neuronal activity and cognitive function. The experiments showed that the high-frequency rTMS treatment group significantly improved the long-term object recognition memory and spatial memory in the AD model mice compared with the control group. However, the effect of transcranial electrical therapy and transcranial magnetic stimulation can only reach the cerebral cortex, and it is difficult to reach the deep brain areas, such as the medial prefrontal lobe, insula, cingulate gyrus and other parts. Repeated use of transcranial magnetic stimulation also has the possibility of causing epilepsy, which will cause potential harm to the human body [19].

4.3.2. Phototherapy. As a physical therapy regimen, Alzheimer's phototherapy instrument is non-invasive and harmless to human body, and has no side effects related to the instrument in clinical trials,

DOI: 10.54254/2753-8818/75/2024.LA19356

and it is safe and reliable. At the same time, the use of the process of no consumables and waste generation, energy saving and environmental protection. In addition, as a physical therapy program, Alzheimer's phototherapy device can be used as a separate treatment program, and can also be combined with other AD therapy programs to provide a better treatment effect, providing more choice space for people to choose AD treatment programs in the future.

The mechanism of action of this therapy is as follows. By deeply studying the physical properties of near-infrared light (NIR) and its effects on cells, On the basis of the NIR spectroscopy studies, Combined with the latest development of frequency light-enhanced brain waves for AD, Innovative ways to illuminate the human head with a specific near-infrared spectroscopy at a specific frequency from both spectrum and frequency, Used to increase brain mitochondrial function and the levels of ATP, promote the breakdown of β -amyloid protein (A β) in the brain of AD patients, reduce the deposition of A β, thus reducing the damage to the nerve cells, improve the repair and regeneration ability of neural tissue, finally, to delay the progression of AD patients, the purpose of improving cognitive function [20, 21].

5. Conclusion

Although the current drugs have a strong prospect, there are still problems of insufficient targeting and specificity, and it will cause harm if accumulated in the body for a long time. Thus, a possible new way both related to protein and specific to overcome the problems is proposed.

ADC, which full name is antibody-drug conjugation, also named biological missile, which was figuratively described for its specificity and effectiveness. It can bind small molecules of bioactive drugs to monoclonal antibodies through a chemical chain, which means a molecule chain held together by a series of chemical bonds, and the monoclonal antibodies act as carriers to transport the small molecules (usually our drugs) to the target cells.

The usage of ADC has two merits. The first comes its function of target delivery. ADC drugs can accurately target specific pathological markers through antibodies, improve the distribution of drugs in the body, and carry out strong killing of target cells, improving the effectiveness of drugs.

Furthermore, Alzheimer's disease is a kind of long-term disease, requiring long-term use of drugs, which means the accumulation of toxicity and may cause many adverse reactions to the body. However, ADC drugs can alleviate this problem. Due to precise targeting, they can significantly reduce the side effects of drugs throughout the body and reduce the damage to normal cells.

However, to design the linker for ADC and to find a method allowing ADC to cross the famous Blood-Brain Barrier are not easy work. Complex process and substantial contribution may be required.

References

[1] Lane, C. A., Hardy, J., & Schott, J. M. (2018). Alzheimer's disease. European journal of neurology, 25(1), 59–70. https://doi.org/10.1111/ene.13439

[2] Soria Lopez, J. A., González, H. M., & Léger, G. C. (2019). Alzheimer's disease. Handbook of clinical neurology, 167, 231–255. https://doi.org/10.1016/B978-0-12-804766-8.00013-3

[3] Kim, B., Noh, G. O., & Kim, K. (2021). Behavioural and psychological symptoms of dementia in patients with Alzheimer's disease and family caregiver burden: a path analysis. BMC geriatrics, 21(1), 160. https://doi.org/10.1186/s12877-021-02109-w

[4] Sacuiu S. F. (2016). Dementias. Handbook of clinical neurology, 138, 123–151. https://doi.org/10.1016/B978-0-12-802973-2.00008-2

[5] Bondi, M. W., Edmonds, E. C., & Salmon, D. P. (2017). Alzheimer's Disease: Past, Present, and Future. Journal of the International Neuropsychological Society : JINS, 23(9-10), 818–831. https://doi.org/10.1017/S135561771700100X

[6] 2023 Alzheimer's disease facts and figures. (2023). Alzheimer's & dementia : the journal of the Alzheimer's Association, 19(4), 1598–1695. https://doi.org/10.1002/alz.13016

[7] Xu Yong, Wang Jun, Wang Hongzheng, Wang Yanjiang, Liu Zhaorui, Yu Jintai... & Tang Bin. (2023). 2023: Alzheimer's disease data and prevention and control strategies in China. Journal of Alzheimer's Disease and Related Diseases (03), 175-192 + 173.

DOI: 10.54254/2753-8818/75/2024.LA19356

[8] Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. Lancet (London, England), 397(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4

[9] Eratne, D., Loi, S. M., Farrand, S., Kelso, W., Velakoulis, D., & Looi, J. C. (2018). Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists, 26(4), 347–357. https://doi.org/10.1177/1039856218762308

[10] Twarowski, B., & Herbet, M. (2023). Inflammatory Processes in Alzheimer's Disease-Pathomechanism, Diagnosis and Treatment: A Review. International journal of molecular sciences, 24(7), 6518. https://doi.org/10.3390/ijms24076518

[11] Pîrşcoveanu, D. F. V., Pirici, I., Tudorică, V., Bălşeanu, T. A., Albu, V. C., Bondari, S., Bumbea, A. M., & Pîrşcoveanu, M. (2017). Tau protein in neurodegenerative diseases - a review. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie, 58(4), 1141–1150.

[12] Liu, B., Kou, J., Li, F., Huo, D., Xu, J., Zhou, X., Meng, D., Ghulam, M., Artyom, B., Gao, X., Ma, N., & Han, D. (2020). Lemon essential oil ameliorates age-associated cognitive dysfunction via modulating hippocampal synaptic density and inhibiting acetylcholinesterase. Aging, 12(9), 8622–8639. https://doi.org/10.18632/aging.103179

[13] Kong, Y., Li, S., Zhang, M., Xu, W., Chen, Q., Zheng, L., Liu, P., & Zou, W. (2021). Acupuncture Ameliorates Neuronal Cell Death, Inflammation, and Ferroptosis and Downregulated miR-23a-3p After Intracerebral Hemorrhage in Rats. Journal of molecular neuroscience : MN, 71(9), 1863–1875. https://doi.org/10.1007/s12031-020-01770-x

[14] Knapskog, A. B., Engedal, K., Selbæk, G., & Øksengård, A. R. (2021). Alzheimers sykdom – diagnostikk og behandling [Alzheimer's disease – diagnosis and treatment]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke, 141(7), 10.4045/tidsskr.20. 0919. https://doi.org/10.4045/tidsskr.20.0919

[15] Passeri, E., Elkhoury, K., Morsink, M., Broersen, K., Linder, M., Tamayol, A., Malaplate, C., Yen, F. T., & Arab-Tehrany, E. (2022). Alzheimer's Disease: Treatment Strategies and Their Limitations. International journal of molecular sciences, 23(22), 13954. https://doi.org/10. 3390/ijms232213954

[16] Wang, R., & Reddy, P. H. (2017). Role of Glutamate and NMDA Receptors in Alzheimer's Disease. Journal of Alzheimer's disease : JAD, 57(4), 1041–1048. https://doi.org/10.3233/ JAD-160763

[17] Vitek, G. E., Decourt, B., & Sabbagh, M. N. (2023). Lecanemab (BAN2401): an anti-beta-amyloid monoclonal antibody for the treatment of Alzheimer disease. Expert opinion on investigational drugs, 32(2), 89–94. https://doi.org/10.1080/13543784.2023.2178414

[18] Ramsay, R. R., Dunford, C., & Gillman, P. K. (2007). Methylene blue and serotonin toxicity: inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction. British journal of pharmacology, 152(6), 946–951. https://doi.org/10.1038/sj.bjp.0707430

[19] Chou, Y. H., Sundman, M., Ton That, V., Green, J., & Trapani, C. (2022). Cortical excitability and plasticity in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis of transcranial magnetic stimulation studies. Ageing research reviews, 79, 101660. https://doi.org/10.1016/j.arr.2022.101660

[20] Semyachkina-Glushkovskaya, O., Penzel, T., Poluektov, M., Fedosov, I., Tzoy, M., Terskov, A., Blokhina, I., Sidorov, V., & Kurths, J. (2023). Phototherapy of Alzheimer's Disease: Photostimulation of Brain Lymphatics during Sleep: A Systematic Review. International journal of molecular sciences, 24(13), 10946. https://doi.org/10.3390/ijms241310946

[21] Tsuchikama, K., & An, Z. (2018). Antibody-drug conjugates: recent advances in conjugation and linker chemistries. Protein & cell, 9(1), 33–46. https://doi.org/10.1007/s13238-016-0323-0