

Mechanism and efficacy of drugs for Alzheimer's disease

Chencheng Ye *

Department of Science, Xi'an Jiaotong-Liverpool University, Suzhou, China

* Corresponding Author Email: Chencheng.Ye19@student.xjtlu.edu.cn

Abstract. Alzheimer's disease (AD) has become into a global concern to public health. Since it was first discovered in 1901, people have studied it for more than one hundred years, and many hypotheses have been proposed. However, its pathogenesis has not been completely revealed. In addition, the treatment and diagnosis of AD is a challenge worldwide, especially in low-income countries. Fortunately, however, some classical hypotheses have their validity, such as cholinergic injury hypothesis, A β cascade hypothesis and abnormal modification hypothesis of tau protein. And the drugs developed on the basis of these classical hypotheses have finally been proved to have therapeutic effects on Alzheimer's disease through continuous experiments by researchers. Among them, Aricept is a drug used in mild AD treating, which acts as cholinesterase inhibitor, while N-methyl-D-aspartic acid (NMDA) receptor antagonist Namenda is used to treat moderate or severe AD. This review reviews the background of Alzheimer's disease and its two available treatment medicines, called Aricept and Namenda, including drug mechanism, efficacy, safety and their pharmacokinetics.

Keywords: Alzheimer's disease, Aricept, Namenda, Mechanism, Treatment.

1. Introduction

Alzheimer's disease (AD) is a clinical syndrome that predominantly affects elderly people and is characterized by gradual deterioration the function of memory and cognitive. Generally, the beginning is slow and irreversible. The World Alzheimer Report 2021 lists dementia as the seventh biggest causing for mortality globally with over 55 million people live with it. The numbers of patients are growing every day, and it is projected to reach 78 million by 2030. The worse thing is, less than 25% of people are diagnosed in the world by estimating and the percentage is excepted to as low as 10% in lower income countries [1]. Therefore, early identification and timely intervention are particularly important to curb the development of the disease.

The A β hypothesis claimed that the cerebral cortex cells are key components of senile plaques in AD patients' brains, the deposit is the central part of the disease, patients with A β by neuron dysfunction or death, plaque formation and nerve fiber tangles after a series of links such as lead neurotoxicity, reflects the whole nerve dysfunction and behavioral changes, resulting in the AD [2]. Neurofibrillary tangles are composed of double-helix filaments in nerve cells, and their main components are abnormally phosphorylated tau proteins. They are intracellular railway-like systems for transporting nutrients, mainly synthesized in neurons, and have great contributions in the synthesis and maintenance for the microtubules (components of the nerve cytoskeleton). Based on the tau propagation hypothesis, tau protein can promote tubulin to form microtubules and maintain its stability under normal conditions. Once it is converted into tau protein, not only the stability of microtubules decreases, but also the related axonal transport disorder and the activity of corresponding neurons decrease, which eventually leads to AD. In short, tau protein abnormally forms neurofibrillary tangles, thus affect transmission of signals in neurons [2].

Aricept is an acetylcholinesterase (AChE) inhibitor. According to researches, it can partially stop acetylcholine from degrading and increase the concentration of ACh in the basal ganglia nerve and cerebral cortex, so as to increase the nerve conduction ability, increase the brain's learning and memory functions, and then improve thinking and memory.

A vital neurotransmitter involved in sensory conduction, motor control and memory storage called Glutamate. It is widespread and abundant in human brain; however, nerve cell apoptosis is deemed to be associated with Glutamate excitotoxicity, caused by overactivation of a glutamate receptor:

NMDA receptor [4]. Namenda is noncompetitive NMDA receptor antagonist, the other name is Memantine HCL, with ability to enter the channel and block it when receptor is overactivated then reduce the Glutamate excitotoxicity.

This review focuses on two kinds of medicines: ARICEPT and NAMENDA with their function and Mechanism. Both of two medicines have been used in treating Alzheimer's disease, which approved by the FDA. The former is developed based on the cholinergic theory and the latter have function in inhibition cell apoptosis.

2. The Pathogenesis of AD

Acetylcholine (ACh) is neurotransmitter related to memory and cognition in human brain, and it is synthesized at nerve terminals by acetyl-CoA and choline catalyzed by ChAT [5]. Meanwhile, upon ACh is released, AChE will metabolize it to choline and acetate, then choline will be transported back to terminals [5]. In Alzheimer's Disease, cholinergic damage is one hypothesis for its pathogenesis. And the key to cholinergic transmission is the balance between acetylcholine synthesis and degradation.

This disease was first discovered by Alois Alzheimer, Germany, in 1901. And in 1906, he reported that brain sections of the patient had two distinct pathological features: amyloid plaques and neurofibrillary tangles [6]. However, the report did not attract attention until it was named as Alzheimer's disease by Emil Kraepelin in 1910 for his authority in the field of mental illness [7]. AD has been discovered for more than a hundred years, at present, there are three recognized pathological features: amyloid β -protein ($A\beta$) deposition, neurofibrillary tangles and massive loss of neurons. Unfortunately, the pathogenesis of AD has not been completely explained, but several hypotheses have been proposed by researchers based on pathological features, such as Cholinergic injury hypothesis, $A\beta$ cascade hypothesis and Abnormal modification hypothesis of tau protein [8].

In 1976, Peter Davies and A. J. F. Maloney proposed cholinergic hypothesis. They compared the activity of neurotransmitter-related enzymes in different regions of the brain between AD patients and controls. Finally, they found that the activity of choline acetyltransferase in amygdala, hippocampus and cortex was significantly decreased, and the concentration of ACh at synapses decreased in AD patients as well. Other key enzymes that related to neurotransmitter synthesis showed activity within normal limits in all brain regions studied in AD [9-11]. According to cholinergic hypothesis, insufficient central cholinergic transmission is a possible pathogenesis for Alzheimer's Disease. Choline deficiency in nerve impulse transmission occurs in 90% of AD patients. In human brain, ACh is a neurotransmitter closely related to learning and memory formation. Meanwhile, acetylcholinesterase (AChE) can metabolize it causing low concentration of ACh [2,5]. Drugs based on this theory, that known as acetylcholinesterase inhibitors (AChEI), relieve the disease by increasing the concentration of ACh, but fail to stop or reverse the pathological process.

In human nervous system, glutamate, is a powerful excitatory neurotransmitter, which is essential for sensory conduction, motor control and memory storage. It is the most widely distributed and abundant transmitter in human brain. If more glutamate released from the synaptic cleft, downstream nerve cells may die of overexcitement, which is called Glutamate excitotoxicity [4]. The reason is the NMDA receptor has the highest calcium ion permeability. For that overactivation of the receptor will lead to massive influx of calcium ions. And eventually leading to neuronal apoptosis. It is found that the apoptosis rate of nerve cells in the brain of AD patients is about 40 times that of normal people, thus one of pathogenesis for Alzheimer's disease may be related to cell apoptosis [4].

3. Aricept

3.1. The mechanism of Aricept

The drug is a white crystalline powder and with its empirical formula is $C_{24}H_{29}NO_3HCl$ with molecular weight for 415.96.

ACh is neurotransmitter involved in cognition, learning and memory, and the brain regulates their levels in the brain through AChE that break them down to achieve normal brain function, and Aricept works on AChE through inhibits it to keep ACh from breaking down, thus increasing acetylcholine levels in the brain [12].

3.2. The Pharmacokinetics of Aricept

Aricept has half-life of approximately 70 hours, which allow patients take it once a day. It can be absorbed completely in gut but slow. Meanwhile, peak plasma levels are reached within 3-4 hours after taken medicine. In addition, take it once a day for around 15-21 days to reach concentration steady state. Liver can metabolize a small amount of Aricept but most is excreted through the urine. The medicine (5mg/day) can be taken by patients who have mild kidney or liver disease, with its few interactions with other medicines [13,14].

3.3. The Effectiveness and Safety of Aricept

A study focused on evaluation of its safety and efficacy when treating the mild or moderate Alzheimer's disease. It was set single-blind, placebo-controlled trial for 89 AD patients, among which 46 patients (21 males & 25 females, aged from 58-87) took Aricept and 43 patients (19 males & 24 females aged from 57-88) took placebo. Meanwhile, 99 AD patients had a self-matched trial, among which 47 males & 52 females, aged from 55-85. The study excluded the presence of other diseases or other drug users that interfered with evaluation of Aricept. The treatment method is taking Aricept 5mg/day orally once a day for 12 weeks. The patients were examined every 4 weeks before and after medication. For the evaluation part, three indicators were used to show drug efficacy, including MMSE to detect the cognitive function of patients, CDR to measure the degree of dementia and Activity of Daily Living Scale (ADL) to test the self-care ability of patients in daily life. The outcomes demonstrate that the control group's MMSE score was much lower than the experimental one's. The MMSE score had significantly improved for self-matched group. In addition, the CDR score of experimental was much lower than that of control and the reductions in CDR scores occurred in the self-matched group as well. For ADL score, the results are similar to that CDR score, experimental group had much lower score than that of control one and self-matched group has a significantly decreasing. Furthermore, safety evaluation, each patient asked to check every 6 weeks before and after medication, including nervous system examination, vital signs examination, function of heart, liver and kidney, electrocardiogram and chest X-ray. The safety inspection display that there are 7 of 145 patients took Aricept (4.8%) had adverse reactions such as dizziness, nausea, loss of appetite. Meanwhile, 2 of 43 placebo patients appeared dizziness. No significant difference was detected. Finally, the vital signs of all patients were stable, and there were no significant changes in blood and urine test and blood biochemical tests before and after treatment [15].

In the control study, it is planned to observe how Aricept effect for neurological function improvement with Alzheimer's disease. There were 91 patients were included. They were split into an observation group of 46 and a control group of 45, which used basic treatment, and the observation group used Aricept on this basis. It was found that prognosis observation group A β 1-42 and Tau protein levels were much lower than those in the control ($P>0.05$) [16].

Good sleep can promote memory, language, thinking and executive ability. Improving sleep disorder can not only improve the cognitive function of patients, but also prevent the occurrence of mental behavior symptoms to a certain extent. Systematic evaluation confirmed there have benefit of Aricept on sleep quality of mild AD patients [17].

Generally, side effects or adverse reactions may occur after treatment with the investigational drug, but they are usually relieved after drug withdrawal. Aricept combined with olanzapine can significantly promote patients recover from the low cognitive function with dementia. Compared with olanzapine alone, the rate of side effects is similar, but the safety is controllable [18].

4. Namenda

4.1. The Mechanism of Namenda

The drug is white powder with its empirical formula is $C_{12}H_{21}N \cdot HCl$ with molecular weight for 215.76.

In 2003, Namenda was approved by the FDA for treating patients with moderate or severe Alzheimer's disease. In those patients, Namenda inhibits the permeability of NMDA receptors by entering the channel and blocking it, then toxic effects of glutamate can be greatly reduced [19]. It has property that quickly dissociate from the receptor with concentration-independent, which means the binding ability of Namenda to be affected at different concentrations while high concentrations do not affect its removal-ability that away from the action site [19]. One advantage for Namenda as a promising medicine is its noncompeting, unlike competitive antagonists such as MK-801, Namenda is noncompetitive NMDA receptor antagonists, which means it does not compete with glutamate for activation sites. Therefore, it has a chance to enter and block the channel only if glutamate successfully activated the NMDA receptor channel. This helps the medicine not to affect normal physiological function under normal conditions. In addition, medium affinity of Namenda is one of its significant attributes. By which reason, it does not accumulate in large numbers around the NMDA receptors. Only when a large amount of glutamate keeps the channel continuously open will it have a greater probability to enter the channel and block it [19]. Thus, the medicine has the ability to block channels in time when glutamate overactivates NMDA receptors.

4.2. The Pharmacokinetics of Namenda

Memantine has an absolute bioavailability of approximately 100% which means it can be almost completely absorbed. It will get peak plasma concentration for about 3 - 7 hours after oral administration and it has a low binding rate of approximately 45% to plasma proteins. Its half-life is 60-80 hours. In addition, about 50% Namenda will be excreted in urine, and the rest becomes metabolites with low NMDA receptor antagonistic activity [20].

4.3. The Effectiveness and Safety of Namenda

There had been three studies submitted to the FDA for evaluation of this medicine. The first study evaluated it for treating moderate or severe AD for a long-term. In this scientific research, 166 patients were selected with their MMSE score is less than 10, GDS score range from five to seven in placebo-controlled trial. At the same time, to measure efficacy, BGP and CGI-C were used. For about treatment method is taking the drug 10 mg each day for 12 weeks. Nevertheless, there were no behavioral improvements observed in this study, functional improvements do indicate that this medication has promise as a potential treatment for people with moderate to severe AD [21].

The second one was in 2003 with similar selection criteria to the first one, but 181 patients took 10 mg drug twice a day for 28 weeks. In addition, Severe Impairment Battery (SIB) was applied as primary efficacy measurement and for secondary efficacy variables, ADCS-ADLsev and the NPI was applied. Moreover, the CIBIC-Plus was used as measurement globally. And the results show that patients who took Namenda had SIB and CIBIC-Plus score significant benefits in statistics compared to those placebos. At the same time, ADCS-ADLsev level for memantine treatment showed significant benefits as well. However, NPI score showed there was no difference was found in these two groups. This study indicated the validity of previous study, that is this drug can partly treat Alzheimer's disease, and while it cannot stop AD progress, it can help them improve their cognitive outcomes [22].

The last study was a combination of Namenda and donepezil treatment. It is a RDBPC trial with 322 patients already took donepezil. Their MMSE score is from 5 to 14, aged 50 or elder. Primary efficacy variables are similar to the previous study, that are SIB and CIBIC-Plus. For secondary efficacy measures, NPI and BGP were used for measurement. The treatment method is half were randomly assigned to memantine and half to placebo, while all patients continued to take donepezil. Finally, it showed that the combination of donepezil & memantine had significant benefits on both

primary and secondary efficacy variables. And this study confirmed what previous studies found with its new finding that behavior of AD patients was improvement [23]. As a matter of fact, it is well tolerated that to transfer from ChEI to memantine treatment [24]. But it is possible to get better treatment outcome from ChEI & memantine treatment [25].

At the same time, research shows that it seems possible to use biomarkers for predicting the sensitivity of Namenda, but the sample size is small, and further research may be needed [26].

It is worth mentioning that the cost-effectiveness of drugs is also very important for the decision of AD scheme. There is no clear conclusion on the cost-effectiveness of this treatment [27].

5. Conclusions

In conclusion, three hypothesis, cholinergic injury hypothesis, A β cascade hypothesis and abnormal modification hypothesis of tau protein, have their validity, and their common feature is that they are all related to neurotransmitter or neuronal damage, which is the basis of drug development. The cholinergic hypothesis proposes that the decrease of ACh can be the underlying pathogenesis of Alzheimer's disease. According to A β cascade hypothesis and Abnormal modification hypothesis of tau protein, AD patients have neuronal dysfunction because of the A β deposition in their brain. Atypical tau protein will lead to the neurofibrillary tangles, axonal transport disorders and the corresponding decrease in neuronal activity, leading to AD.

Aricept is acetylcholinesterase (AChE) inhibitors to maintain ACh levels in the brain of AD patients. Although it does not stop the progression of the disease, it can eventually alleviate mild symptoms of Alzheimer's disease. Meanwhile, NMDA receptor antagonist, Namenda, is noncompetitive antagonist and used in moderate or severe Alzheimer's disease treatment. It works by entering the channel and blocking it. There are two advantages that make Namenda be effective medicine: its noncompetitive and medium affinity. These two properties allow it not to affect normal physiological function under normal conditions, and to block channels in time when glutamate overactivates NMDA receptors. Meanwhile, it has been shown that it has a significant effect on AD when used alone or in combination with cholinesterase inhibitors.

At present, there is no drug that can halt the progression of Alzheimer's disease completely. In the meantime, when making drug decisions, we should not only analyze the efficacy, but also consider cost-effectiveness, safety and patient compliance. The clinical diagnosis and treatment of AD is still a subject with great challenges. Many studies are still in the exploratory stage. In addition to the pathogenesis involved in this article, it may also be related to the virus theory, genetic factor theory and other mechanisms. Further analysis of the pathogenesis of AD and exploration of more drugs will have benefit prevent and treat AD in the future.

References

- [1] Gauthier S, Rosa-Neto P, Morais JA, & Webster C. 2021. World Alzheimer Report 2021: Journey through the diagnosis of dementia. London, England: Alzheimer's Disease International.
- [2] Liu P-P, Xie Y, Meng X-Y, Kang J-S. History and progress of hypotheses and clinical trials for Alzheimer's disease. *Signal Transduction and Targeted Therapy*. 2019/08/23 2019;4(1):29.
- [3] Alonso AD, Grundke-Iqbal I, Barra HS, Iqbal K. Abnormal phosphorylation of tau and the mechanism of Alzheimer neurofibrillary degeneration: sequestration of microtubule-associated proteins 1 and 2 and the disassembly of microtubules by the abnormal tau. *Proc Natl Acad Sci U S A*. Jan 7 1997;94(1):298-303.
- [4] Olajide OJ, Gbadamosi IT, Yawson EO, et al. Hippocampal Degeneration and Behavioral Impairment During Alzheimer-Like Pathogenesis Involves Glutamate Excitotoxicity. *J Mol Neurosci*. Jun 2021;71(6):1205-1220.
- [5] Purves D, Augustine GJ, Fitzpatrick D, et al., editors. *Neuroscience*. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. Acetylcholine.
- [6] Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde". *Clin Anat*. 1995;8(6):429-31.

- [7] Kraepelin E. Psychiatrie: ein Lehrbuch für Studierende und Ärzte.
- [8] Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci.* Oct 1991;12(10):383-8.
- [9] Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry.* Feb 1999;66(2):137-47.
- [10] Fotiou D, Kaltsatou A, Tsiptsios D, Nakou M. Evaluation of the cholinergic hypothesis in Alzheimer's disease with neuropsychological methods. *Aging Clin Exp Res.* Oct 2015;27(5):727-33.
- [11] Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM. Alzheimer's disease: Targeting the Cholinergic System. *Curr Neuroparmacol.* 2016;14(1):101-15.
- [12] Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev.* Jan 25 2006;2006(1): Cd005593.
- [13] Wilkinson DG. The pharmacology of donepezil: a new treatment of Alzheimer's disease. *Expert Opin Pharmacother.* Nov 1999;1(1):121-35.
- [14] Seltzer B. Donepezil: a review. *Expert Opin Drug Metab Toxicol.* Oct 2005;1(3):527-36.
- [15] Dantao Peng, Xianhao Xu, Qingyun hou, et al. Efficacy and safety of Aricin in the treatment of mild to moderate Alzheimer's disease [J]. *Chinese Journal of Neurology*, 2002,35 (01): 19-21
- [16] Tiesheng Liang. Clinical observation of donepezil on the improvement of neurological function in patients with Alzheimer's disease [J]. *Journal of Aerospace Medicine*, 2020,31 (05): 566-568
- [17] Blackman J, Swirski M, Clynes J, Harding S, Leng Y, Coulthard E. Pharmacological and non-pharmacological interventions to enhance sleep in mild cognitive impairment and mild Alzheimer's disease: A systematic review. *J Sleep Res.* Aug 2021;30(4): e13229.
- [18] Zheng W, Sun X, Liu J. Efficacy of Donepezil Hydrochloride plus Olanzapine for Senile Dementia and Its Effect on the Recovery of Cognitive Function. *Evid Based Complement Alternat Med.* 2022; 2022:4156312.
- [19] Thomas SJ, Grossberg GT. Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. *Clin Interv Aging.* 2009; 4:367-77.
- [20] Periclou A, Ventura D, Rao N, Abramowitz W. Pharmacokinetic study of memantine in healthy and renally impaired subjects. *Clinical Pharmacology & Therapeutics.* 2006;79(1):134-143.
- [21] Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry.* Feb 1999;14(2):135-46.
- [22] Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med.* Apr 3 2003;348(14):1333-41.
- [23] Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res.* Feb 2008;5(1):83-9.
- [24] Waldemar G, Hyvärinen M, Josiassen MK, Kørner A, Lehto H, Wetterberg P. Tolerability of switching from donepezil to memantine treatment in patients with moderate to severe Alzheimer's disease. *Int J Geriatr Psychiatry.* Sep 2008;23(9):979-81.
- [25] Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *Jama.* Jan 21 2004;291(3):317-24.
- [26] Swerdlow NR, Kotz JE, Joshi YB, et al. Using Biomarkers to Predict Memantine Effects in Alzheimer's Disease: A Proposal and Proof-Of-Concept Demonstration. *J Alzheimers Dis.* 2021;84(4):1431-1438.
- [27] Pardo-Moreno T, González-Acedo A, Rivas-Domínguez A, et al. Therapeutic Approach to Alzheimer's Disease: Current Treatments and New Perspectives. *Pharmaceutics.* May 24 2022;14(6)