Alzheimer's Target and the Treatment Progression of Classic and New Clinical Drugs

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Abstract. Alzheimer's Disease (AD) is a traditional neurodegeneration disease in the world. In 1906, this disease is first described by German Neuroscientist, Alois Alzheimer, and it is named by this scientist, 'Alzheimer'. Although 4-5% of patient carry AD at middle age, which is the Early- onset Alzheimer's Disease. Normally, the average onset age of AD is above 65. The symptom of AD including dementia, loss of memory, cognitive impairment and eventually it will accelerate the death of aged people. There are two pathological factors that cause people have AD's symptom: Amyloid Plaques and Neurofibrillary Tangles (NFTs). Focus on that, this review will mainly introduce two medicine treatments that target those two factors: The classical cholinergic medicine Donepezil and The Novel Lithium medicine that has been proved to treat AD since 2012. This article will describe the pathology of AD briefly; focus on those two medicines, the functional mechanism, effectiveness to AD and limitation will be described also.

Keywords: Alzheimer's Disease, Lithium Treatment, Donepezil, GSK-3, Cholinergic Medicine.

1. Introduction

Alzheimer's Disease (AD) is classified as a category of neurological disorder caused by consecutive deterioration in the function of neurons, with insidious early symptoms. Clinical symptoms of AD involve memory loss, weight loss, seizures, wandering, and personality changes. It is incurable, irreversible, and has multifactorial pathogenesis. In the line with World Health Organization (WHO), nowadays, over 55,000,000 patients carry AD globally, and the number is continuing to grow at a rate of almost 10 million new cases per year.[1] In late-stage AD, patients have lost their ability to community and have to depend completely on the care of others. In 2022, AD has become the sixth deadly illness of the whole world. Since patients lost cognition, they cannot do anything in their daily life and mean time, they body is getting deteriorated, patients with late-stage AD often develop fatal complications including aspiration pneumonia, cardiovascular disease, pulmonary embolism, cachexia, and bedsore. Although aging is a significant factor, AD is not a normal phenomenon of aging, and increasingly earlier onset AD has been reported, which refers to the condition of AD with an age of onset younger than 65.[1]

The impact of AD is spreading to surmount a wider population. Under such circumstances, there has been an urgent need for drugs which can help with the treatment of the disease. Unfortunately, although researcher had never stopped exploring and learning more about the disease, the research and development in this field has been stagnant for the past 18 years. Since the first hypothesis of the pathology of AD proposed 40 years ago, there are various hypothesis seeks for the proper explanation of this disease, including the cholinergic hypothesis, tau hyperphosphorylation hypothesis, oxidative stress hypothesis, inflammatory factors hypothesis, and amyloid cascade hypothesis.[2] Nevertheless, the fundamental causes and effective treatments are still ambiguous.

There is a compound called acetylcholine, it can be found throughout the whole brain system and function as a neurotransmitter. In the brain of AD carrier, researchers found that the cholinergic neurons decline are associate with acetylcholine synthesis and metabolise, and cholinergic loss become a hallmark of AD.[3] Based on that discovery, the earliest of the drugs for AD are function to

inhibit metabolism of acetylcholine. And Donepezil is one of the classical drugs, function by inhibiting the acetylcholinesterase.[4]

Lithium treatment is also a classic drug in psychiatric disease, it has been used as the main drugs to treat the bipolar disorder for 5 decades. In AD treatment, Lithium is known as inhibitor of the Glycogen synthase kinase-3 (GSK3), an essential enzyme in AD, because this enzyme can phosphorylate the tau protein and the phosphorylation it induced in vitro is comparable to the actual presented in AD carrier's brain. In addition, lots of study suggested that long term treatments of Lithium can slow down the cognitive and functional deficits of patients.[5] Moreover, both Donepezil and Lithium treatment are proved have positive affection on the cognition of AD patients by systematic review and meta-analysis.[6]

This paper will focus on introducing the function and their function mechanism of Donepezil and Lithium in the AD pathology. And those two drugs will be compared refer to their different medicinal property and clinical treatment. On the other hand, this review will have a discussion on the limitation, function efficiency and clinical potential for Lithium and Donepezil.

2. Pathological Characteristics of AD

In AD, there are two pathological hallmarks: amyloid plaques, also known as Abeta, and neurofibrillary tangles (NFTs). For amyloid plaques, it is established by amyloid peptides. In patient's brain, amyloid precursor protein (APP) will process aberrantly to generate those peptides; NFTs is formed mainly by the tau protein hyperphosphorylation. Tau is a cytoskeleton protein, commonly it is responsible for maintaining the microtubules as a stable form in axons, and it is abundant in the neurons. However, it contains more than 39 phosphorylation sites, and NFTs formation are mainly because of the tau hyperphosphorylation.[7]

2.1. GSK-3:

Interestingly, GSK-3 involves in both two mechanisms, because GSK-3 contains the kinase function and its signaling can abnormal process the APP. GSK-3β in several studies are proved as the key contributor for the tau phosphorylation. On tau protein, there are 28 sites can be phosphorylated by GSK-3 in vitro, and most of them are AD-relevant sites. [7] In vivo studies, in transgenic mouse, overexpression of GSK-3β will induce the mouse has the symptom of neurodegeneration. Same as the mouse, in another Drosophila research, overexpression of tau and GSK-3β will induce the same result.[8]

Glycogen Synthase Kinase-3 is critical enzyme in neurodegeneration, and it is classified as a serine/threonine kinase. There are two isoforms for GSK-3, GSK-3α and β, in adults, those two kinases are mainly expressed in brain. However, in neurodegeneration area, GSK-3β are well studied and GSK-3α are commonly ignored, the reason is that GSK-3β are expressed more abundantly in adult hippocampus, and normally AD will affect this area in its early stage.[8] To activate GSK-3, it has to be pre-phosphorylated and pre-dephosphorylated. On GSK-3 protein, there are two inhibitory sites at N & C-terminal domains respectively, before activation, those two domains will be phosphorylated first to create a inhibiting domain to block the function of GSK-3, and after that this domain will be dephosphorylated to activate the GSK-3 enzymatic activity.[8,9] In addition, the GSK-3 activation also needs another phosphorylation at tyrosine residue, for GSK-3β, this site will be Tyr216, and phosphorylation of this residue will be more relevant for AD, because some studies said that active tyrosine phosphorylated GSK-3 show co-localization to a special AD's hallmark, Neurofibrillary tangles (NFTs).[9,10]

Among those GSK-3β phosphorylated sites on tau protein, some sites need a primary phosphorylation, and this work is done by cyclin-dependent kinase 5 (Cdk5). In AD, the activator of Cdk5, p35, will undergo proteolysis and form p25. And this new substance can over-activate Cdk-5 and eventually result to tau hyperphosphorylation.[11] However, some researchers suggest the overactivation of Cdk-5 mediated by p25 will inhibit the GSK-3β in transgenic mouse with young

age.[12] On the other hands, in elder transgenic mouse, the aged mutant p25 will not inhibit the GSK-3β, and this mutant p25 even improve the GSK-3β activity and thus eventually enhance the tau hyperphosphorylation. And that phosphorylation will be inhibited by the GSK-3β blocker, which means the Cdk-5 is not the main pathogenic kinase for AD.[7]

On axon, microtubule is an essential component for axonal transportation, and tau will normally bind to the microtubule to maintain its stability. Once the tau undergoes hyperphosphorylation, it will dissociate from microtubule. Kinesin is a motor protein for transporting cargo from soma cells to axon, and tau protein binding on microtubule will decrease the kinesin mobility.[13] On a research studying the GSK-3β and axonal transportation, researchers find out that, as tau phosphorylated by GSK-3β, the kinesin transportation of hyperphosphorylated tau is increasing.[7] That may explain why in AD, the GSK-3β phosphorylated tau existed in axon.[8]

GSK-3β also contribute a key role on amyloid plaque formation, the relationship of GSK-3β, amyloid peptides and APP is a loop. Amyloid peptides will firstly block the inhibitory domain of GSK-3β to activate it and after that activated GSK-3β will involve in processing of abnormal APP. And eventually, amyloid peptides are produced by APP. This GSK-3β affection may also show a potential linkage between the Amyloid plaques and NFTs.[8]

3. Lithium

Lithium is a classical treatment used in psychiatric disease and has been studied for a few decades. Before researchers discovered its function for Alzheimer's disease, Lithium always is contained in the medicine for bipolar disorder. On the other hand, Lithium can inhibit the activity of GSK-3, which is an essential enzyme in AD's pathology. After 2012, Lithium is confirmed to be medicine for Alzheimer's disease.[5]

Lithium treatment in pharmacology means the medicine contain the Lithium salt. Lithium chloride is a medicine approved for treating psychiatric disease. The main function of Lithium is that it can reduce or inhibit the activity of abnormal expressed or overactivated substance in certain signal pathways, such as the pathway related to GSK-3, therefore it shows effectiveness for AD's therapy. Regarding to GSK-3 activity, there are several evidence shows that with the treatment of Lithium, the neurotoxicity mediated by the amyloid plaque will be normalized. Similarly, the tau hyperphosphorylation, leaded by GSK-3β also can by inhibited by the lithium treatment.[14]

3.1. Mechanism

The inhibition mechanism of Lithium to GSK-3 has two pathways, indirect inhibition, and direct inhibition. The basic concept of Lithium mediated inhibition to GSK-3 is that the Li+ ion acts as an uncompetitive inhibitor for the co-factor magnesium to GSK-3. Magnesium ion and lithium ion has similar ionic radius, which is 0.60 and 0.65 Angstroms respectively. Due to this characteristics, Lithium ion can invade to the magnesium binding site with low affinity on GSK-3, and since the charge density of lithium ion is lower, it can disrupt catalytic function of the enzyme. This is the mechanism of direct inhibition. For indirect inhibition, when GSK-3 is being activated, protein kinase B (also named Akt) is responsible for inhibitory phosphorylating the GSK-3, and this phosphorylation will inactive the GSK-3. However, the activation of the D2 dopamine receptor (D2R) and other G protein coupled receptors (GPCR) will facilitate the Akt, beta-arrestin 2 (βArr2), and protein phosphatase 2A (PP2A) to form a signaling complex. And this complex will inactivate the Akt, thus lead to activation of GSK-3. Lithium, in this case, can disrupt the formation of this signaling complex that may because the interaction between Akt1 protein and βArr2 requires magnesium.[15]

3.2. Effectiveness

Lithium as a medicine for psychiatric disease has been used for a few decades. In last ten years, researchers keep studying the effectiveness of lithium to the patients who suffered cognitive impairment. In a trial that contains placebo test to random individuals, they verified the effectiveness

of Lithium to mild cognitive impairment (MCI) and AD carriers. The result showing Lithium reduce the cognitive depression significantly, and even the approved cholinergic drugs have similar effect size of this medicine.[16] In addition, another in vitro Animal study trials have shown that lithium also cause the affection of glucose metabolism on mouse's hippocampal when the mouse carry AD.[17]

Furthermore, in a Meta-analysis included 3 randomized controlled studies (n=232), in this analysis, researchers assess the lithium effectiveness AD's patients and people who carry cognitive impairments. The feedback is, compare with the placebo, Lithium involved cognitive recoveries of patients gets a significant enhancement in AD and cognitive dysfunction (MD = -0.41, 95%CI = -0.81 to -0.02, P = 0.04, I2 = 47%).[16]

3.3. Limitation

Elder patients may be more sensitive to Lithium side effects, including hand tremor and nausea. Moreover, Lithium also can induce the thyroid and renal dysfunctions, and those two symptoms need to be managed with medical staff. For thyroid dysfunctions, hormone replacement can be used to deal with, but for renal dysfunction, the drug discontinuation may be required.

On the other hand, in another clinical trial, the MCI patients that has lower doses of Lithium requirements show better tolerance for Lithium, and the side effects are commonly mild and transient.[5] Therefore, Lithium treatment with lower doses may be safer.

4. Donepezil

Donepezil(2-((1-Benzylpiperidin-4-yl) methyl)-5,6-dimethoxy-2,3- dihydro-1H-inden-1-one) was first approved as a treatment of various degrees of AD in 1996 by the Food and Drug Administration of United States. It reversibly selectively inhibits AChE with 1260 times greater selective affinity for AChE than for BuChE[18]. By controlling the activity of AChE, the concentration of ACh can enhance, increasing cell signaling and cholinergic function of the central nervous system.

4.1. Metabolism

Its metabolism takes place primarily in the liver. 79% of the recovered dose can be discovered in the urine, with the remaining 21% being discovered in the faeces.[19] In the metabolism of donepezil, an isoenzyme named cytochrome P-450 plays the most significant role, with CYP-2D6 assisting by playing a minor role.[20] Three metabolism pathways of donepezil are distinguished: O-dealkylation and hydroxylation, glucuronidation, hydrolysis and N-oxidation. The products of O-dealkylation and hydroxylation M1 and M2 are the most abundant in the extracted metabolites. The glucuronidation of M1 and M2 results in M11 and M12. The second most abundant products are M4, the product of hydrolysis, and M6, the product of N-oxidation.[19]

4.2. Mechanism

The precise mechanism of donepezil is still not entirely explained by current progress of research. However, it is evident that it involves in controlling the cholinergic system function loss in AD patients' brain. It can effectively prevent the hydrolysis of Ach by binding of the active sites of AChE. The peripheral anionic site (PAS) and the catalytic anionic site are the two primary active dur interaction binding sites in AChE.[21] Donepezil is an N-benzylpiperidine-based acetylcholinesterase inhibitor (AChEI). It consists of three parts, a dimethoxy indanone part, a piperidine part, and a benzyl ring.[22] Dimethoxy indanone binds to the PAS of AChE and connects with N-benzylpiperidine. The latter binds with 4 amino acid residues, which are Tyr-70, Asp-72, Tyr-121, and Tyr-334, attaches to the CAS.[21]

Studies have also supposed some noncholinergic functions of donepezil. Donepezil can upregulate the nicotinic receptors in the cortical neurons, reversibly inhibit voltage-activated sodium currents, and can delay rectifier potassium currents. However, it is still unknown how these could contribute to clinical treatments.[23]

4.3. Effectiveness

Numerous experimental results show that the percentage of patients who received donepezil after a certain period met the criteria for clinical deterioration was lower than the placebo group. The mean decrease in Mini Mental Status Examination (MMSE) and ADAS-cog scores was greater in the placebo group in studies. The blood flow of the prefrontal and parietal lobes in the experimental group usually also presents significant increase, while the placebo group usually shows a significant decrease comparing to before. These results suggest that although the us of donepezil cannot avoid the worsening of AD, the control of the severity of the worsening is still beneficial.

Tkacheva et al. conducted a study to assess the efficacy of donepezil monotherapy and donepezil and akatinol memantine combination therapy with 35 patients of mild stage of AD for 12 months. Every three months, the patients were evaluated using a combination of the Mini Mental State Examination, the Frontal Assessment Battery, and memory tests to monitor the progression of the disease.

The patients were assessed with a combination of Mini Mental State Examination, Frontal assessment battery, and memory tests every 3 months to track the progression of the disease. In 3 months of the therapy, patients who received combination treatment demonstrated improvement on almost all the neuropsychological examinations.[24]

A study[25] in 2020 explored the most effective treatment method among memantine monotherapy, donepezil monotherapy, and combination therapy of the two. The efficacy of the three different therapies where evaluated based on four perspectives after assessing the results of 54 researches carried out in Asia, Europe, and North America: cognition, global assessment, daily activities, and neuropsychiatric symptoms. The combination therapy demonstrated the most significant improvement in the ADAS-cog scores (MD 5.01, 95% Crl -0.86 to 10.73). Combination therapy is more effective than donepezil or memantine monotherapy when using the alternation in CGI for the overall assessment. The data for daily activity combined ADCS-ADL and ADL. Combination therapy (MD 16.27, 95%Crl -8.06 to 40.52) demonstrated a better effect than using donepezil or memantine separately. Neuropsychiatric symptoms showed better improvements in patients receiving combination therapy comparing to patients receiving monotherapy. The study concluded that memantine and donepezil combination therapy is more effective from the four perspectives of evaluation for the progression of the disease. However, this is accompanied by the increase in cost.

As the population of AD patients increases, there are more patients from low-income group who needs treatment. Many studies have analyzed the cost-effectiveness of difference treatment for AD. A study compared the cost-effectiveness of donepezil, galantamine, rivastigmine, and memantine. Among them, donepezil is the most cost-effective for mild to moderate AD. Although the total cost of galantamine is slightly lower than donepezil, donepezil can give slightly greater QALY gains. For moderate to severe stage of AD, donepezil less cost-effective than memantine.[26] However, with new discoveries on the effectiveness of some drugs, this result might not be the most up to date.

4.4. Derivatives

Derivatives of donepezil can be classified into 3 categories by the part replaced from the original structure: replacement of the methylene linker between the indanone part and the piperidine part, replacement of the indanone part, and replacement of the piperidine part.[21] A series of experiments on donepezil derivatives has demonstrated most of the derivatives can effectively inhibit the activity of AChE. Additionally, they exhibited effective ADMET, blood-brain barrier penetration, and antioxidant activities.[27] Two of these derivative compounds presented a discernable impact on restoring the scopolamine-induced memory loss and showed minimal hepatotoxicity in mice, suggesting they might be suitable therapeutic candidates for treating AD. [27]

4.5. Limitation

Donepezil can only ameliorate a series of cognitive symptoms, as ACh are still continuously undergoing hydrolysis and will eventually reach the point where it the level of ACh left in the brain

cannot compensate for the cholinergic neurotransmitters' deficit and the loss of functioning brain cells even with the aid of drugs.

Although donepezil is well tolerated, its effects on the central nervous system can still cause various side effects. The inactivation of AChE can result in overstimulation of nicotinic and muscarinic receptors, causing problems such as muscle spasms, epilepsy, ataxia, and tremors. Donepezil may cause bradycardia and cardiac conduction abnormalities, thus patients with cardiac conduction abnormalities may experience syncope due to vagal properties. Cholinesterase inhibitors can increase gastric acid secretion and should be used with caution in patients with ulcers. Donepezil and other cholesterol-mimetic drugs has the potential danger of triggering seizures. For patients with history of benign prostatic hyperplasia, the drug might cause or exacerbate bladder outflow obstruction. It can exaggerate muscle relaxation during succinylcholine-induced anesthesia. Due to its choline-mimicking properties, it could cause adverse effects for patients with history of asthma or obstructive pulmonary disease. Patients at risk for rhabdomyolysis should also use donepezil with caution.[23]

For elderly patients, who make up the majority of AD patients' population, the impact of these adverse effects on the quality of life and other aspects of health should not be ignored. Although there are very few reports of severe and life-threatening side effects, donepezil should always be used cautiously under instruction.

5. Conclusions

AD is a common multiple neurodegenerative disease, especially in people are aged. The main hall mark of AD are intracellular NFTs and senile plaques formed by extracellular amyloid aggregation, and GSK-3 accounts a key role in those mechanisms. The treatment for AD still needs further studies, traditional donepezil can enhance the function of cholinergic nerve, based on the inhibitory effect of acetylcholine hydrolysis process, can obviously increase the acetylcholine levels play a role, alleviate symptoms of AD's patients, can be used alone or with other drug, however, it can't cure the disease in the end. Low-dose lithium therapy may get better therapeutic outcomes for AD treating and its prodromal stages. However, further evidence-based evidence of its therapeutic effect is needed. Currently used therapies can only improve cognitive worsening and behavioral depreciation in patients. More evidence-based studies will be conducted in the future to gain a deeper understanding of AD to provide more ideas for drug development.

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