Pathogenesis of Alzheimer's disease and its treatments: A systematic review

Yuxuan Lou[1, a, *, †], Shiyuan Sun[2, b, *, †], Jiangqi Tan[3, c, *, †]

[1] College of Letters and Science, University of California Davis, Davis, CA 95618, United States
[2] College of Electrical, Energy and Power Engineering, Yangzhou University, Yangzhou, Jiangsu, 225127, China
[3] School of construction machinery, Chang'an University, Xi'an, Shanxi, 710018, China
[†]These authors contributed equally.

Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by loss of memory and cognition. In this review article, three main pathogenesis of AD were described: Amyloid-beta hypothesis, Tau protein hyperphosphorylation and Neurotransmitter decrease hypothesis. Specifically, amyloid-beta accumulation can be detrimental for nervous system for Amyloid-beta hypothesis, while Tau protein hyperphosphorylation can cause the breakdown of nerve cells. With regard to Neurotransmitter decrease hypothesis, it is deemed as the direct reason to cause Alzheimer's disease. On top of that, mainstream treatments therapy and their features, advantages and disadvantages are discussed. Firstly, medicine treatments corresponding to its pathogenesis are introduced. Secondly, gene therapy is also demonstrated which alleviates Alzheimer's disease be means of gene modification, inactivation and immune regulation. Finally, the stem cells therapy is also described as well as other therapies. Based on our analysis, combined therapy should be put into practice to achieve a better effect. Moreover, more knowledge about AD pathogenesis is required for researchers, which provides theoretical basis and reference for treatments. These results shed light for future research of AD.

1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that involves loss of memory and thinking, which is prevalent in aged people. As the world's population ages, the number of people with AD is expected to increase from 50 million today to 152 million by 2050 [1]. Contemporarily, due to the increasing number of AD patients, AD has caused a huge burden to many countries and societies. Therefore, understanding the pathogenesis of AD and finding effective treatment methods are of great significance to human society.

There are three main causes of AD. The first hypothesis is that Aβ protein over aggregates. Excessive aggregation of Aβ protein can combine with metal ions in cell fluid to oxidize neurotransmitters, leading to deactivation of neurotransmitters, i.e., brings about AD [2]. Secondly, hyperphosphorylation of Tau protein destroys microtubule tissue, resulting in loss of nerve cell function and eventually nerve cell death [3]. Last but not least, decrement of some types of neurotransmitters might be the cause of AD.

The main treatments of AD include 1) Medicine therapy; 2) Genetic therapy; 3) Stem cells therapy. Until now, medicine is the widest and the most effective way in the treatment of AD. However, the therapeutic effect of drugs is not satisfying and some of them possess side effects at present. Genetic and stem cells therapy are still

in the experimental stage, i.e., more researches and experiments are needed to put them into practice. There are also some auxiliary therapies, e.g., transcranial magnetic stimulation, deep brain stimulation and some other intervention treatments. Moreover, Chinese medicine may be an effective way for the treatment of AD, which is proved to improve some symptoms of AD according to literatures.

In order to better understand the pathogenesis of AD and cure it effectively, the current prevalent pathogenesis of AD and mainstream treatment methods were summarized in this article. These results might act as a guide to future researches on new treatments of this disease.

2 Pathogenesis

2.1 Amyloid-β protein hypothesis

Many researchers proposed the amyloid peptide hypothesis, suggesting that the accumulation of Amyloid-β (Aβ) peptides in the brain may be the fundamental cause of Alzheimer's disease. A large number of studies have shown that under pathological conditions, abnormally folded proteins can accumulate on nerve cell membranes. Under normal conditions, the Aβ precursor protein (APP) is sequentially digested by β-crepeptidase and γ-

*Corresponding author: [a]aellou@ucdavis.edu,
[b]jiangwei@yzu.edu.cn, [c]gcjxxyxb@chd.edu.cn

crepeptidase to produce Aβ. Aβ can be decompressed and removed in a constant manner and only exists in a trace soluble state in the brain. However, in AD patients, the metabolic balance of Aβ is destroyed and Aβ is overexpressed because of pathological reasons, resulting in spontaneous oligomeric formation and deposition of senescence plaques [4].

Nam et al. [2] went a step further to find out how Aβ causes AD. In the brains of patients with AD, high concentrations of metals (e.g., 0.4mM Cu, 0.9mM Fe, 1mM Zn) are found in senile plaques composed of Aβ aggregates. In addition, copper has been reported to reach high micromolar concentrations at the synaptic sites after neuronal excitation, indicating a possible interaction between copper and Aβ in the synaptic fissure [5]. Cu (I/II) and Aβ have binding affinity. Cu (I/II) and Aβ act as oxidants to oxidize a variety of neurotransmitters, e.g., monoamine neurotransmitters, dopamine and norepinephrine. The complex and dynamic environment in which the synaptic cleft occurs suggests a potential interconnection between three elements in AD pathology: Cu (I/II), Aβ and neurotransmitters. Cu (I/II) and neurotransmitters released after neuronal excitation are important components in synapses that regulate the activation of neurotransmitter receptors and maintain signal transduction. Under pathological conditions, Aβ may be associated with neurodegeneration through interactions with these two components [6].

2.2. Tau protein hypothesis

Tau protein is a hydrophilic protein that is commonly existed in solution. According to circular dichromatography analysis, it appears as a random curl protein [7]. The primary function of Tau protein is to provide stability to the microtubules at the end of axons and dendrites [8].

Tau protein is usually a "naturally unfolded" protein that plays an important physiological role in maintaining microtubule stability. Increased level of modification leads to self-aggregation and hyperphosphorylation of Tau protein. Hyperphosphorylation of Tau may regulate the conformation and charge of the protein, which eventually leads to the exposure of the microtubule binding domain. Thus, it achieves self-aggregation and oligomerization of Tau protein. Besides, these clumped tau proteins eventually convert into nerve fiber tangles (NFTs) [3]. Hyperphosphorylation of tau protein leads to a loss of axon transport, i.e., permanent instability of the microtubules [9]. Patients with AD had a relatively high amount of abnormal or hyperphosphorylated tau protein compared to normal controls. In addition, these misfolded tau protein lose the primary function of microtubule stability and increase the aggregation effect, which are found to be potential neurotoxins. Ultimately, impaired tau-microtubule function contributes to loss of synaptic plasticity and axonal transport results in cognitive deficits. In addition, p-tau activates microtubule-cut-off protein (e.g., Katanin), which worsens the microtubule assembly process. Abnormal phosphorylation of Tau protein is the main event of pathological enhancement of Tau protein [3].

To sum up, adverse modification and disruption cause Tau protein hyperphosphorylation. Thus, it leads to Tau protein oligomerization, which eventually forms NFTs. This results in microtubules being exposed and disintegrating, contributing to the death of nerve cells, eventually AD.

2.3. Neurotransmitters' decrease hypothesis

Neurotransmitters play an important role in keeping and maintaining human's synaptic functions that are fundamental for people [10]. Many scientists believed that the direct reason that causes AD is the decrease level of some neurotransmitters. With the development of pharmacology, acetylcholine, dopamine, γ-aminobuytyric acid (GABA), and N-methyl-D-aspartate (NMDA) has been proved that are associated with the pathogenesis of AD. A typical example is acetylcholine. Impairment of cortical cholinergic neurotransmission contributes to Aβ pathology and increases Tau protein phosphorylation. Selective activation of M1-M3-MACHR rather than M2-M4-MACHR (muscarinic acetylcholine receptor) increases SAPPα secretion and decreases total Aβ formation [11]. Other neurotransmitters have not been found to be directly related to the pathogenesis of AD, but they may play an indirect role in the pathogenesis of AD [12].

Compared with the control group, the detection values of GABA, glutamic acid, 5-hydroxytryptamine (5-HT) and acetylcholine in the experimental group decreased, and the differences were statistically significant according to Ref. [13]. Through the correlation analysis of various neurotransmitter levels and MMSE score in AD patients, the neurotransmitter levels of GABA, 5-HT and Ach were positively correlated with MMSE score.

Ravi Rajmohan and P. Hermachandra [14] discussed the relationship between Aβ and hyperphosphorylated tau protein with the pathogenesis of AD. They suggested that Aβ and hyperphosphorylated Tau protein have negative effects on neurotransmission, axonal transport, etc.. On this basis, it can block and inhibit the release of neurotransmitters, i.e., the amount of neurotransmitters decreases.

3 Treatment of AD

3.1 Medical treatment

3.1.1 Medicine concerned with Aβ

Due to the important role of Aβ in the pathogenesis of AD, it has become a research and development hot spot of AD drugs in recent years. A large amount of Aβ deposition in the brain tissue of AD patients will harm the cells in membrane, synapse and axon. The mechanism of drugs based on Aβ include: 1) Regulating the production of Aβ; 2) Increasing the eliminating of Aβ; 3) Inhibiting the accumulation of Aβ [15].

At present, immunotherapy for Aβ is mainly divided into passive immunity and active immunity, where current

researches are more about passive immunity. For example, solanezumab, a kind of Aβ monocloning antibody (Aβ-specific MAb), was developed by Eli Lilly company for the treatment of mild AD [16]. So far, the research of active immunity vaccine is represented by Novartis drug CAD106 [17]. CAD106 can significantly activate Aβ specific antibody, i.e., inhibits the accumulation of Aβ in the brain. CAD106 has passed the safety, efficacy and tolerance tests [18]. β-secretase (BACE) is the key enzyme in the production of Aβ. Besides, inhibition of the enzyme will greatly reduce the production of Aβ. Some drugs, for instance, MK8931、AZD-3293、E2609 and CNP520 have been used for clinical trials but with little satisfying results, where most of them end in failure [17].

3.1.2 Medicine concerned with Tau protein

Drugs targeting Tau protein are being actively developed, which includes at least 4 types [19]. 1) Tau protein immunotherapy refers to the use of Tau protein antibody or vaccine to eliminate the NFTs caused by abnormal phosphorylation of Tau protein, so as to prevent or treat AD. 2) Tubulin stabilizer is conducive to the removal of the block of neurotransmitters when Tau protein is abnormally phosphorylated. 3) Tau protein kinase inhibitors helps inhibit the produce of kinases, are associated with Tau protein abnormal phosphorylation. 4) Tau protein aggregation inhibitor can inhibit the forming of paired helical filaments (TAI), i.e., improves signal transmission between nerve cells.

Aci-35 is a liposome vaccine against abnormally phosphorylated tau protein. Theunis C et al. [19] found that the expression of specific anti phosphorylated Tau protein IgG was increased and showed good safety and effectiveness in animal trails of Aci-35. Panza F et al. [20] confirmed that TPI-287, targeting stable tubulin, may be effective for AD treatment. Lovestone S et al. [21] found that Tideglusib, as a GSK-3 β inhibitor, will significantly improve the intelligence score of patients denoting good safety. Gauthier S et al. [22] found that LMTM (leuco-methylthioninium bis(hydromethanesulphonate)), a small molecule Tau protein aggregation inhibitor, can maintain the activity of inhibiting Tau protein aggregation in vitro and in vivo.

Although the failure of anti-Aβ therapy leads to the query of "amyloid protein" hypothesis, and the drug research and development in Tau protein has been paid more and more attention. However, most of them are in the early stage of clinical research [17].

3.1.3 Medicine concerned with Neurotransmitter

The decrease of neurotransmitters in central nervous system is related to the impairment of memory. Therefore, increasing the neurotransmitter (e.g., acetylcholine) in human central nervous system may help improve the symptoms of AD. Meanwhile, there are also some Non-cholinergic drugs which can improve the abnormality of non-cholinergic neurotransmitters in the brain. Several drugs based on neurotransmitter are shown in table 1.

Table 1. Drugs based on Neurotransmitter and explanation.

Drugs	Explanation
Lecithin [23]	A kind of prodrug of acetylcholine, can increase the synthesis and release of acetylcholine
Pilocarpine [23]	Directly stimulates the Postsynaptic receptor
Cholinesterase inhibitors [23]	Inhibits the activity of cholinesterase, reduces its hydrolysis and increases the acetylcholine between synapses
Donepezil [24]	Suitable for the treatment of mild to moderate AD
Tacrine [25]	Has been withdrawn by the food and Drug Administration (FDA) due to its severe hepatotoxicity
Rivastigmine [23]	Significantly inhibits the activity of AChE (Acetylcholinesterase) in the hippocampus and cerebral cortex
Memantine [23]	NMDA antagonist
Dextromethorphan quinidine [26]	Used for PseudoBulbar affect
L-deprenyl [26]	Monoamine oxidase inhibitors
Propyl theophylline [26]	Adenosine receptor antagonist

Nowadays, the efficacy of anti-AD drugs for the treatment of acetylcholine deficiency is not significant. Meanwhile, medicine concerned with neurotransmitters also have some side effects [26]. For instance, Taclin may possess the hepatotoxicity and cause side effects on digestive tract, and Memantine can cause dizziness, headache, diarrhea and fall. Donepezil also possesses the side effects (e.g., insomnia, fatigue and spasm) in some clinical trails. Nevertheless, recently Anti-AD drugs based on neurotransmitters have achieved some progresses while lots of researches and developments on other anti-AD drugs almost end in failure. At present, drugs approved to be used in clinical treatment are almost Neurotransmitter-based. Anti-AD drugs based on neurotransmitters will have good application prospects and deserve more further researches [24].

3.1.4 Medicine concerned with other Pathogenic factors

Moreover, researchers found that drugs for other diseases may help improve the symptoms of AD. Inflammatory response can promote the deposition of Aβ that causes neuron loss and cognitive dysfunction, which plays a crucial role in the development of AD [27]. Additionally, probiotics will reduce the toxic effect of bacterial secretion on the central nervous system, i.e., reduces the deposition of Aβ and NFTs in the brain. Furthermore, AD patients have metabolic disorders of sugar, protein, nucleic acid and lipid. The drugs of improving cerebral blood circulation provide a new choice for the prevention and treatment of AD [23]. Insulin signaling pathway also plays an important role in regulating the deposition of Aβ and the phosphorylation of Tau protein [28]. Several drugs and related explanation are listed in table 2.

Table 2. Other drugs for the treatment of AD.

Drugs	Explanation
Nonsteroidal Antiinflammatory Drugs(NSAIDs) [29]	Can significantly reduce the risk of AD, long term use of NSAIDs causing a series of adverse reactions such as liver and kidney damage
Berberine [30,31]	Shows good anti-inflammatory effect in treatments of AD, no obvious adverse effect even in the high dose application
Sodium Oligomannate Capsules [26]	Improves the cognitive function of patients, efficacy and safety need to be verified
Hydergine [23]	Improves glucose utilization, increases information transmission and improves intelligence
Piracetam [23,32]	Enhances nerve transmission and promotes energy metabolism
Oxiracetam [23,32]	Enhances nerve transmission and promotes energy metabolism
Insulin combined with oral hypoglycemic drugs [28]	Slows down the decline of cognitive function in AD patients

3.2 Genetic therapy

Different from medical treatment, genetic therapy, which is aimed at the abnormal gene itself, refers to transfer complementary normal genes or therapeutic functional genes to the defective or diseased cells, so as to achieve the purpose of AD treatment [33]. The strategies of AD genetic therapy include 1) gene inactivation; 2) gene modification; 3) immune regulation, etc. Gene inactivation refers to the use of antisense technology to specifically block gene expression characteristics in order to inhibit the expression of some harmful genes, so as to achieve the purpose of AD treatment. Gene modification is to introduce the target gene into the diseased cells or other cells. The expression products of the target gene will modify the function of the defective cells or enhance some of the original functions. Immune regulation refers to the introduction of antibody, antigen or cytokine genes into patients to change the immune state.

Matsumoto [34] found that after using a DNA vaccine ym3711 against a variety of Aβ fragments, Aβ $_{1.42}$, AβpE$_{3.42}$, Aβ oligomer and Aβ fiber in the brain of TG mice were significantly reduced. Benmenachem Zidon et al. [35] used genetic engineering to transfer anti-inflammatory factor gene into neural stem cells and then transplanted into AD mice. They found learning and memory functions of the mice were better than that of the mice transplanted with neural precursor cells only. Wu et al. [36] confirmed that hNGF expressing gene modified neural stem cells can integrate into the body and replace damaged or lost nerve cells.

So far, genetic therapy for AD still faces many problems, e.g., the safety, stability and effectiveness of gene expression. Further research of genetic therapy for the treatment of AD is needed for clinical application and promotion. The main factors restricting the development of genetic therapy are as followed: 1) The exact pathogenesis of AD is unclear; 2) Lack of suitable transgenic vector [37]. Whereas, with the completion of the genome project, the further elucidation of the pathogenesis of AD and the discovery of more effective target genes, genetic therapy will become an effective way to treat AD.

3.3 Stem cells therapy

Neural stem cells (NSCs) are primordial cells with self-renewal and multi-directional differentiation potential. Studies have found that NSCs can not only differentiate into various types of nerve cells to replace the missing nerve tissue, but also produce a variety of cytokines. Specifically, it contains brain-derived neurotrophic factor, nerve growth factor and glial derived neurotrophic factor. Besides, it promotes synaptogenesis and regulates its plasticity in order to effectively improve the cognitive, learning and memory functions of AD animals. Generally, there are two main ways: (1) endogenous way that induces the proliferation and differentiation of endogenous NSCs, i.e., damaged nervous system can repair itself; (2) Exogenous approach which direct transplantation of exogenous NSCs to replace the defect of nerve tissue or implantation of genetically engineered cells [38]. mesenchymal stem cells (MSCs) is a kind of non-neuronal adult stem cell derived from mesoderm, which is easy to expand and have multiple differentiation potential. MSCs is a kind of method for cell replacement therapy because of its rich source, simple material and avoiding ethical problems and immunogenic response [39].

Baron et al.[40] found that IFN-γ can improve neurogenesis of dentate gyrus in adult mice, i.e., improves their spatial learning and memory ability. Chen et al. [41] found that after NSCs was transplanted into the hippocampus of 12 month old transgenic AD mice, the spatial memory and learning ability of the experimental group was significantly better than that of the control group in the water maze experiment compared with the control group. Lee et al. [42] transplanted MSCs from bone marrow into the hippocampus of APP/PS1 transgenic mice. It resulted in the activation of endogenous microglia and macrophages, the decrease of Aβ and hyperphosphorylated Tau protein, and the improvement of spatial learning ability and memory.

In recent years, some progresses have been made in the treatment of AD with stem cells, while stem cells therapy still stay in the stage of animal experiment [38]. We believed that with the further understanding of NSCs or MSCS, the application of NSCs and MSCs in the treatment of AD or other neurological diseases will become a reality in the near future.

3.4 Other therapies

Apart from the therapies discussed above, some new methods may help cure AD entered people's field of vision. Transcranial magnetic stimulation (TMS), as a new clinical treatment, has made remarkable achievements in the treatment of mild to moderate AD. The mechanism of TMS for AD treatment is not clear. Some scholars believe

that TMS treatment can promote glucose metabolism and cerebral cortical blood flow, improve cerebral blood circulation, and provide material basis for brain metabolism [43]. Additionally, Deep bain stimulation (DBS) improves the symptoms of AD by reshaping the structure, metabolism and neural circuits of different brain regions in AD patients. Besides, these brain regions or brain networks are related to cognitive functions such as memory [44]. Moreover, Chinese medicine, including Compound Chinese Traditional Medicine (CCTM), Monomer and extract of traditional Chinese Medicine and acupuncture, has been proved by a large number of researches the treatment effects for AD [45]. Furthermore, some intervention treatments (e.g., training, psychotherapy and music therapy) have been proved the improvement of the symptom of AD. The features of these therapies are concluded in Table 3.

Table 3. The features of different therapies.

Therapy	Features
TMS [43]	No trauma and pain, an effective auxiliary treatment
DBS [44]	A minimally invasive, reversible and adjustable neuromodulation technology
Chinese medicine [45]	Almost has no side effect, but how to establish the close relationship between various detection indexes and the theory of traditional Chinese medicine and make it convincing is still a problem
Intervention treatment	A good choose for combined treatment

4 Conclusion

In summary, we explicated the definition of AD, the present situation of AD, the hypothesis of the pathogenesis of AD, and various treatments for AD. Besides, future research direction of AD was conjectured in the review. For pathogenesis of AD, three main types are summarized: the redox reaction of Aβ to neurotransmitters, the hyperphosphorylation of Tau protein and the reduction of the number of some neurotransmitters. In the first hypothesis, the Aβ binds to certain metal ions in the cell fluid and redox the neurotransmitters. The aggregation of Aβ protein will enhance the occurrence of this redox reaction. The second hypothesis is that the hyperphosphorylation of Tau protein causes the microtubules becoming entangled, leading to the death of nerve cells. It is worth mentioning that the phosphorylation of Tau protein can effectively modify the structure of Tau protein. Moreover, the modified Tau protein can be used for other physiological activities. Only the hyperphosphorylation of Tau protein can lead to the collapse of microtubules and the oligomerization of Tau protein [4]. With regard to the third hypothesis, the decline of neurotransmitters will cause the AD, which has been proved by experiments.

So far, there is still no special ways to cure AD. There are still various difficulties in AD drug research and development: 1) Lack of clinical application indicators of drugs; 2) No suitable animal research model at present; 3) Many key mechanisms have not been fully revealed and understood. Therefore, the basic theoretical researches on the pathogenesis, as well as the development and research of drugs for the treatment of AD are both essential. Moreover, combined therapy should be put into practice to achieve a better effect, e.g., the genetic and stem cells therapy or other auxiliary methods should be integrated into the whole treatment strategy. Additionally, from a large number of researches, we find that some other factors also are related to AD. Some of them are psychological status, the levels of blood sugar, cerebral inflammation, insulin and brain metabolic level. Thus, we should pay attention to these factors when make a treatment plan. Moreover, new methods ought to be explored to cure AD (e.g., Chinese traditional medicine therapy), which becomes a more and more popular topic in the treatment of AD.

To understand and cure AD effectively, scientists must conduct further research. First, it's important to understand why the Aβ aggregates in large numbers. Because the occurrence of AD is accidental, plenty of results also show that the occurrence of AD is not absolutely determined by genes. Therefore, the environment may be the main factor for origination of AD. Scientists should start to investigate from the life and diet habits of patients before the disease, which may lead to new discoveries. Second, the causes of Tau protein hyperphosphorylation and the path to avoid it should be investigated in order to develop new drugs. These results provide reference value for the future research.

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