Treatment for alzheimer's disease: The present and future

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Abstract. Alzheimer's disease (AD) is a growing global health crisis, however, there are currently very few effective treatments for it. All existent treatments serve only to ameliorate the symptoms of AD instead of curing it. With the deepening of the disease pathology in recent years, there have been many studies and clinical trials that aim to discover new disease-modifying therapies. Nanoparticle drug delivery platform is a promising path for its high penetration rate across the blood brain barrier, while heat shock proteins provide a new strategy to target the mutant proteins that cause AD. These novel therapies may help us better treat and potentially cure AD, but many of them are still in their early stage of development and their side effects are still unknown. A truly effective treatment for AD is still years ahead.

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that impairs the brain's cognitive and memory function in the elderly population. There are several proposed pathologies for AD, including neurofibrillary tangles (NFTs) formed by hyper-phosphorylated tau protein and aggregation of extracellular proteins like β -amyloid ($A\beta$) peptide. (Fig. 1) [1] The specifics of how these abnormalities lead to the symptoms of AD are still unclear, but it is theorized that the insoluble protein oligomers can cause an inflammatory effect, and the subsequent oxidative damage kills many neurons surrounding the aggregated proteins. [2] Even though genetics can directly affect how proteins behave, it is

being proven in numerous studies that ageing, environmental, and dietary risk factors may contribute the most when it comes to developing AD. An unhealthy diet with high fat and high sugar content, air pollution, and poor sleeping are common risk factors found in AD cases. [3,4] Among these, ageing plays the most significant role. There is currently no treatment that targets these mechanisms and provides a cure for AD. All the existing therapies only seek to mitigate the symptoms and prolong the patients' life. [5] This article will review the current therapies for AD and discuss some of the future treatments currently being proposed or developed..

2 Current Treatments

Fig.1. Aetiology of Alzheimer's disease.

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2.1 Cholinesterase Inhibitors

One of the major hypotheses for why patients with AD have a lowered cognitive function is the cholinergic hypothesis. It is theorized that impaired brain functions are caused by reducing acetylcholine's secretion (ACh). ACh is a neural transmitter that plays a crucial role in the passing of signals across the synapses. In the brain, ACh is responsible for numerous physiological processes such as memory, learning, and attention. In this theory, the decreased level of ACh in the brain can explain the cognitive dysfunction that comes with AD. Thus, inhibiting acetylcholinesterase (AChE) to increase ACh's level becomes a feasible solution to mitigate the symptoms. AChE is the main enzyme that breaks down ACh. By introducing acetylcholinesterase inhibitors (AChEI) to the brain, ACh's degradation is decreased, and ACh can accumulate and restore normal cognitive function. [6] Tacrine was the first AChEI to be approved by the FDA for clinical treatment of AD. However, Tacrine met immediate setbacks after its introduction to the market. It had severe side effects, including hepatotoxicity, and its therapeutic effect was not ideal. [7] Several other AChEIs were also developed and introduced to the market after the failure of Tacrine, such as donepezil and galantamine. These products exhibit low cytotoxicity and increased therapeutic efficacy, and they are still being used for the symptomatic treatment of AD [8].

2.2 N-methyl D-aspartate Receptor (NMDAR) Antagonists

NMDAR, when activated, allows the influx of Ca^{2+} , which eventually leads to the activation of gene activation necessary for the formation of long-term potentiation (LTP). It is theorized that the overactivation of NMDAR in patients with AD can cause a critically elevated level of Ca^{2+} inside the neurons and consequently leads to overstimulation of glutamate. Glutamate is the main excitatory amino acid in the CNS, and the constant stimulation eventually causes excitotoxicity and cell death. NMDAR antagonists can block NMDAR's functional site and control the level of activation. So far, memantine is the only NMDAR antagonist approved by the FDA to be used for clinical treatment of AD. It is a low-affinity uncompetitive antagonist, and it is proven to be effective in blocking NMDAR without interfering with normal synaptic functions. Memantine is usually used to treat severe AD and often used alongside AChEI. [9-12]

3 Future Treatments

3.1 Nanoparticle Delivery Systems

Nanoparticle drug and gene delivery therapies for AD are gaining significant attention because of their high therapeutic efficacy. Traditional drug delivery platforms (oral, injection) are mostly passive drug delivery methods and thus make drug difficult to get to the brain, especially with the protection of the blood-brain-barrier (BBB). BBB is a layer of endothelial cells that surrounds the central nervous system (CNS). It is highly selective and tightly regulates the substances that can cross into and out of the CNS. [13] Hydrophobic molecules can pass the BBB with relative ease, and hydrophilic molecules can only cross the BBB with the aid of special transporters. Because of this, a popular candidate for nanoparticle drug delivery inside the BBB is a liposome. The liposome is a hydrophobic, biocompatible, and biodegradable material, and it is one of the most common materials used for nanoparticle drug delivery platforms. [14]

3.1.1 $\text{A}\beta$ -targeting Liposome Particles

One example of nanoparticle drug delivery therapy for AD is liposome particles multi functionalized with phosphatidic acid (PA) and modified apolipoprotein E (mApoE). PA has been proven to bind to $\text{A}\beta$ oligomers and disassemble them for plasma excretion. mApoE is a ligand that can pair with multiple receptors present on the BBB. [15-16] The therapy is still under development, but preliminary animal studies have shown that the AD mice treated with this therapy exhibited better cognitive function recovery [17]

3.1.2 Liposomal mApoE2 Gene Delivery System

Liposomal gene delivery is also a viable treatment method for AD. It is recently discovered that ApoE2 is beneficial for AD prevention for its role in clearing $\text{A}\beta$ peptide aggregation. The isoform ApoE4, however, can contribute to the progression of AD. Thus, a liposomal gene delivery platform is developed to deliver ApoE2 plasmid DNA (pDNA) into the neuronal cells to stimulate more ApoE2 production. The pDNA is enclosed inside the particle, and the particle surface is functionalized with penetratin (Pen) and glut-1 targeting ligand mannose (MAN). (Fig. 2) MAN can help the particle target and cross the BBB, while Pen aid in cellular internalization. The in vitro studies showed that the cells treated with this particle exhibited high ApoE2 expression, which can be a promising treatment in the future. [18,19]

Fig. 2. Schematics of the liposomal mApoE2 nanoparticle

3.2 Heat Shock Proteins (Hsps)

Heat shock proteins are intracellular proteins that protect cells from elevated temperatures. They do so by binding to and prevent other proteins from misfolding under heat. Similarly, most neurodegenerative diseases, including AD, are caused by protein misfolding and aggregation. So, we might be able to harvest the unique function of Hsps and use them to target the key proteins in AD. There are already several Hsps that can prevent A β peptide and tau misfolding. [20]

3.2.1 Hsp60

Hsp60 is a large heat shock protein that is critical in mitochondrial protein folding. How it participates in the disease progression of AD is not yet clear. Still, it is theorized that it could be overexpressed by active microglia and lead to neuronal cell death by elevated pro-inflammatory factors. Thus, inhibiting the expression of Hsp60 and activated microglia might be a potential solution for treating AD. Mizoribine and pyrazolopyrimidine EC3016 are both examples of molecules that can inhibit Hsp60. They can bind to the ATPase active site on Hsp60 and prevent the protein from functioning. But the pharmacology of this theory is still unclear and needs more investigation. [20]

3.2.2 Hsp70

Hsp70 has been proven in a recent study to bind to A β 42 and prevent self-aggregation. In the animal study, Hsp70 exhibited two functions: protecting neurons from A β 42 neurotoxicity and synaptic loss. Hsp70 functions by activating microglia, insulin-degrading enzyme, and tumor growth factor- β 1 (TGF- β 1), which can degrade A β peptide. Hsp70 can also bind to tau and its mutant form to prevent aggregation. [21] By examining AD brain tissue samples, an overexpression of Hsp70 was observed, and there could be a connection between this and the activated glia cells and stressed neurons. Hsp70 could also be associated with extracellular deposits in

AD. Several anticancer drugs, which target Hsp70's ATP-binding site, could be used to treat AD. YM-01 is an excellent Hsp70 inhibiting compound. It binds to Hsp70 and prevents proliferation. It was developed as a derivative of MKT-077, a similar compound but with high toxicity and low bioavailability. [22-24]

3.2.3 Hsp90

Hsp90 is another large heat shock protein that is thought to take part in AD's disease progression. Hsp90 regulates tau phosphorylation and dephosphorylation. Inhibition of Hsp90 leads to a decrease in tau kinase activity and tau phosphorylation. Like Hsp70, inhibitors of Hsp90 are also previous anticancer drugs. Animals studies have identified several Hsp70 inhibitors that worked in mouse models. 17-AAG is one of the most promising one among them. It is a derivative of geldanamycin (GA) but with lower cytotoxicity and better bioavailability. Pochoxime C is also an Hsp70 which gained attention for its safety and therapeutic efficacy in animal studies. From these studies, Hsp has been proven to be promising candidates for AD treatment. [25-27]

3.3 Nutraceuticals

Natural compounds, mostly from plants, have been used to treat diseases for thousands of years, and recently researchers are turning to these products for neurodegenerative diseases. Some nature-sourced molecules have shown therapeutic effects and are in clinical trials for AD. Below, we will introduce several nutraceuticals from traditional Chinese folk medicine.

3.3.1 Allium Compounds

Allium compounds are abundant in garlic (*Allium sativum*), a vegetable that is cultivated around the world. It is widely used in cooking, but it has also been used to treat cardiovascular diseases in China for 3000 years. [28] Allium compounds mainly consist of diallyl sulfide, s-allyl-L-cysteine sulfoxides (Allin), S-allyl-L-cysteine and allicin (diallyl thiosulphate). [29] These molecules are

organo-sulfurous and contribute to the unique smell and taste of fresh garlic. From many studies, Allium compounds have shown anti-inflammatory, antitumor, cardioprotective, antioxidant properties. [30-32] As mentioned above, AD is mainly caused by misfolded tau protein, which aggregates and leads to the upregulation of proinflammatory agents, activating the NF- κ B cascade and downregulating ERK, CREB, and Akt pathways. But one of the Allium compounds, s-allyl cysteine (SAC), has been proven to downregulate the NF- κ B cascade thus slowing down AD progression. [33,34] In addition, SAC has been proven to repair neuronal damage and aid in memory function remediation. [35,36] Allium compounds also have little side effects and are considered generally safe by the FDA.

3.3.2 Turmeric

Turmeric (*Curcuma longa*) is a plant that mainly grows in Southeast Asia. It is mostly consumed as a spice, but it has also been used as a medicine for thousands of years. Its active compound, curcumin, has long been identified as a strong antioxidant, anti-inflammatory, and anti-tumor agent. [37] Recently, curcumin has become a rising star in the field of AD treatment for its anti-amyloid properties. [38] In several studies, curcumin has shown the effect of inhibiting A β production and aggregation while increasing A β clearance. In addition to its anti-A β amyloid property, curcumin also serves as an anti-inflammatory compound that reduces the inflammation caused by tauopathy. Curcumin can inhibit the enzyme cyclooxygenase (Cox-2), 5-Lipoxygenase (5-Lox), the enzyme responsible for prostaglandin synthesis, and NF- κ B, a neuroinflammatory marker. [39,40]

3.3.3 Ginseng

Ginseng (*Panax ginseng*) is another herb that has been used as a medicine for thousands of years. Ginsenosides, the active compounds of ginseng, have shown neuroprotective and memory enhancement effects. [41] Some ginsenosides can prevent A β plaque formation by inhibiting beta secretase 1 (BACE1), an enzyme that is critical for A β formation. [42] As mentioned above, one of the major current treatments for AD is AChEIs, ginsenosides Rb1, Rb2, Rc, Re, Rg1, and Rg3 have also shown AChE inhibiting properties. [43] Rg2 can protect neurons from oxidative stress by reducing the Ca²⁺ and reactive oxidative species (ROS) levels. Rb1 and Rb5 can inhibit NF- κ B and reduce the expression of anti-inflammatory factors like IL-1B, IL-6, and TNF- α . [44]

4 Conclusion

As the number of AD cases around the world continues to rise, it has become a global health issue that requests increasing effort to find a solution. However, despite the massive amount of time and capital that have been spent, the current clinical treatments still only provide

symptomatic amelioration. The primary reason behind it is that we still do not fully understand the pathology of AD. There are many explicit theories, but the deeper we dig, the more complex the disease becomes. Cholinesterase inhibitors and NMDA antagonists like galantamine and memantine work well to enhance patients' memory, but there is no way to pause the disease progression. Fortunately, as more details of AD pathology are being uncovered, researchers are finding alternative ways to target A β and tau pathologies. Liposome nanoparticles carrying mApoE and phosphatidic acid can cross the BBB and breakdown A β plaques, while the particle can also carry ApoE2 gene to increase the expression of ApoE2 and achieve the same effect. Heat shock proteins are also promising candidates that aid in protein function maintenance. Nutraceuticals from traditional Chinese medicine are also attracting much attention for their great potentials in treating AD. In conclusion, the key to treating AD lies behind the full understanding of the disease. The novel treatments that target A β and tau pathologies may be able to stop the disease progression instead of slowing it down.

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