Amyloid-B In Alzheimer's Disease: Hypothesis, Mechanisms, Corresponding Therapies

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Abstract: Alzheimer's disease (AD) is the main cause of dementia [1]. AD is a kind of neurodegenerative disease which is unsolvable nowadays. The amyloid-β cascade hypothesis is one of the older hypotheses about the mechanism of the disease. At present, researchers' understanding of the genetic factors of the hypothesis extends to the study of the function of specific genes. The influence of environmental factors on the disease is also being actively studied, and other further research is being conducted through the holes in this hypothesis. Based on the amyloid-β cascade hypothesis, researchers proposed the possible pathogenesis of AD, and further discovered many different treatments. For example, immunotherapy-based drugs aducanumab and non-steroidal anti-inflammatory drugs have been shown to be effective. Aβ receptor antagonist is now in phase III trial. This paper will introduce the structure of amyloid-β and amyloid plaque and explain the amyloid cascade hypothesis from both genetic and environmental factors. The focus is on the development background of related drugs and the therapeutic effects of the two main proposed therapies for AD. In the future, further studies on the pathogenesis of AD are still required to find targets for intervention. The introduction and summary of the hypothesis and corresponding therapies may make the achievements of the scientists in this direction clearly visible.

1. Introduction

Alzheimer's disease (AD) is one of the most debilitating neurodegenerative diseases of old age. As the average life expectancy increases and the population ages, the number of people suffering from and even dying from AD keeps increasing. This not only afflicts a large number of families but also puts enormous strain on health and social care systems. Nowadays there are 6.2 million Americans over the age of 65 affected by this. If effective preventions and treatments cannot be developed and applied, this number will grow to 13.8 million in 2060. 2019 is the most recent year for which data are available. According to demographic data from 2000 to 2019, the death rate from AD is increasing rapidly when being compared with other common kinds of diseases, such as heart disease, stroke, and Aids because deaths caused by AD increased by more than 145 percent [2].

What makes AD so intractable can be explained in terms of both its characteristics and unclear mechanism. Alzheimer's disease is a kind of progressive disease, which means the severity is proportional to the time. It can cause a serious decline in people's cognitive competence until dementia. Early symptoms include some mild memory loss and cognitive impairment. As the disease progresses, patients' spatial cognitive function will gradually decrease. Some mental symptoms will develop, such as delusions, disturbed sleep, and frequent mood swings. In the later stages of the disease, their brains are severely damaged. They can barely move their bodies, have almost no langrage competence, and face significant problems with both short and long memory. The typical characteristics of the disease

are amyloid-β plaques that accumulate extracellular in the cerebral cortex and limbic areas of the human brain and intracellular neurofibrillary tangles composed of abnormal proteins [3]. However, the specific mechanism of AD is still in the stage of exploration. The amyloid-β cascade hypothesis is one of the systematic guesses that has been studied for a long time. Based on this hypothesis, a variety of therapies have been studied to alleviate the symptoms of AD. Perhaps there are some loopholes in this hypothesis, but it provides a theoretical basis for the treatment methods of AD. Its defects can also strongly promote the in-depth study of other hypotheses. This paper will present a series of research on the principle and treatment of disease related to the amyloid cascade hypothesis by introducing the latest advances in disease research and related therapies in detail.

2. Amyloid-β and amyloid plaque

Deposition of amyloid-β (Aβ) in the human brain is thought to be the beginning of the progressing of AD, which is associated with plaques and tangles in the brain. This progress can begin 15-20 years before the onset of clinical symptoms, mainly relating to a decrease in the brain's ability to eliminate the peptide [4]. Aβ is produced by proteolytic processing of a transmembrane protein which is expressed in a variety of tissues, especially in synapses, amyloid precursor protein (APP) [5]. This process is done by β- and γ- secretases, which is known as the amyloidogenic pathway. APP also has a processing called the non-amyloidogenic pathway. In this kind of pathway, APP is cleaved by A Disintegrin and Metalloprotease (ADAM) family proteases. This process yields soluble APP alpha and the membrane-tethered C83 fragment instead of Aβ [6].

The protein polymer of Aβ can exist in a variety of interchangeable forms, like monomers, dimers, oligomers, protofibril, fibril, and amyloid plaques. These different modalities form a locally reversible cycle. Only fibril and amyloid plaque are insoluble. They will form the protein deposits that can be observed [6].

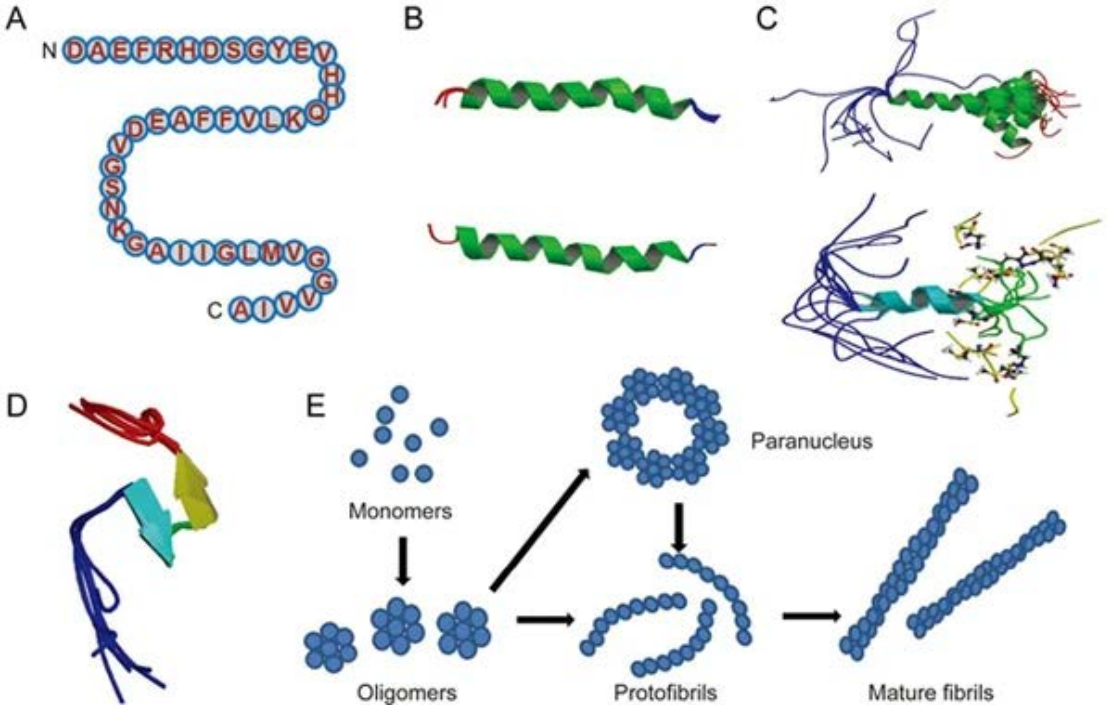

Figure 1. Structures of Aβ monomer, fibril, and oligomers [5].

3. The amyloid cascade hypothesis

The amyloid–β cascade hypothesis is mainly focused on the imbalance between produce and cleavage of Aβ, which leads to the improper accumulation of Aβ plagues in different areas of the brain. This hypothesis presumes that aggregation of Aβ peptide is correlated with the extent of the loss of neurons. Although the demo to neurotoxicity of Aβ–peptide is difficult through the majority of the

animal model because it suggests there is an intermediate part between amyloidosis and neurodegeneration [7].

But with three decades of research have made on the Amyloid–β cascade Hypothesis, we can still summarize and complete a rational system in this hypothesis, which can be divided into two different sections to explain the specific mechanism of the aggregation of Aβ eventually lead to AD, which is the genetic factors and the environmental factors.

3.1 Genetic factors

(1) Gene of the amyloid precursor protein

The amyloid precursor protein is a kind of dependent receptor. The research has found this gene on chromosome 21, and if it comes to a mutation, the promotion of Aβ-peptide may be caused by the processing capability of secretases or other biology characteristic change in Aβ, for example, the increasing fibrillation, the resistance to oxidative stress. However, we still know relatively little about APP's physiological roles.

(2) Presenilins (PSEN)

The intramembrane presenilin proteins make form the α-, β-, γ-secretase complexes, which can cleave APP and generate A. Presenilins 1 and 2 are mostly found in neurons and are encoded by the PSEN 1 and PSEN 2 genes on chromosomes 14 and 1, respectively [7]. The conversion of A from its more abundant A40 isoform to the more toxic A42, and thus a higher than normal A42: A40 ratio, has been linked to late-onset AD [8]. Familial mutations in PSEN 1 and PSEN 2, as well as an overproduction of APP, are a leading cause of A from its more abundant A40 isoform to the more toxic A42, and thus a higher than normal A42: A40 ratio, has been linked to late-onset AD [8].

3.1.3 Apolipoprotein E (ApoE)

ApoE is a 299-amino-acid lipoprotein encoded by the ApoE gene on chromosome 19. Human ApoE is found in a variety of organs, with the liver expressing the most, followed by the brain. ApoE is extensively expressed in astrocytes and microglia in the brain, as well as in stressed neurons. The ApoE gene has three allelic variants: ApoE 2, ApoE 3, and ApoE 4. ApoE 2 encodes Cys residues at 112 and 158, ApoE 3 encodes a Cys residue at 112 and an Arg residue at 158, and ApoE 4 encodes Arg residues at both sites. ApoE isoforms may differ structurally and functionally because of differentia charge characteristics of the variable amino acid residues in ApoE alleles [9]. ApoE has been demonstrated to play both a dependent and independent function in AD pathogenesis in recent studies. Both astrocytes and microglia create ApoE, which is then lapidated by ABCA and converted into lipoprotein particles. Lapidated ApoE sticks to an isoform-dependent way with soluble Aβ (E2>E3>E4) in the extracellular space, influencing the development of parenchymal amyloid plaques and A transit within the CNS. Different components of the LDL receptor (LDLR and LPR1) endocytose ApoE into distinct cell types inside the brain, the way of facilitation the cellular uptake of Aβ is through an ApoE composite lipoprotein linked to Aβ.

Amyloid precursor protein gene, PSEN, ApoE and other gene mutations or the existence of allele mutants lead to important changes in the synthesis or decomposition of Aβ peptides, resulting in AD disease. However, it is still unclear whether these target genes can be intervened to treat or delay the progression of AD in the future, and more research is needed.

3.2 Environmental factors

(1) Corticotrophin-releasing hormone

Corticotrophin-releasing hormone (CRH) is a 41-amino-acid protein. It influences the hypothalamic-pituitary-adrenal (HPA) axis, which helps to regulate the stress response. The CRH-1 and CRH-2 receptors are where CRH works. CRH-1 is dispersed throughout the brain, whereas in the brain, there can find expression of CRH-2 splice variant, with the supreme level of CRH-2 in the heart and skeletal muscles [10]. Hippocampal CRH-1 has been discovered to mediate stress in learning, whereas a hinder process of learning may cause by the lateral intermediate septum. Previous research has indicated that CRH levels in the Cerebro Spinal Fluid (CSF) are lower in Alzheimer's patients when compared to sex and age-matched healthy controls [7]. In clonal cells and primary cerebellar

neurons, higher levels of CRH enhance sAPP production in a CRH-R1-dependent way. The regulation of CRH level may enhance α-secretase expression while reducing β-secretase expression [11]. The study of molecular mechanisms reveals that CRH plays a neuroprotective effect in Alzheimer's disease.

(2) Angiotensin II

Renin cleaves angiotensinogen to generate angiotensin I. Angiotensin converting enzyme (ACE) then converts Angiotensin I into Angiotensin II. In physiological and pathological situations, many organs are mostly affected by angiotensin II. AT1 and AT2 are two angiotensin receptor subtypes, which have been identified based on their selective selectivity [7]. Angiotensin II has been linked to Alzheimer's disease. Angiotensin II overproduction is associated with higher pressure of blood, the increasing of brain inflammation, and all of the known risk factors for Alzheimer's disease. AT-1 receptor antagonists, on the other hand, have been shown to impede similar processes [12]. ICV injection of Angiotensin II to Sprague Dawley rats has shown a considerable rise in A production in recent years. Through the manipulation of multiple components of the APP processing pathway, this in vivo investigation established the important function of Angiotensin II in amyloidogenesis [12].

(3) Somatostatin

Somatostatin (SST), also known as somatostatin-14 and somatostatin-28, comes in two molecular forms. These two types can be found in neural tissues over the human body. The G-protein coupled receptor is the tool somatostatin works through, which is receptor-mediated. Somatostatin has been shown to affect the learning and memory processes. Somatostatin levels have been discovered to be lower in the brain and CSF of Alzheimer's patients. The content of somatotrophin release inhibiting factor (SRIF) in the frontal cortex of post-mortem AD brains decreased considerably with cognitive impairments. In addition, a somatostatin shortage caused changes in hippocampus neprilysin activity and localization, as well as an increase in the amount of Aβ peptide [13].

(4) Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino-acid peptide found in the brain. It has a wide range of physiological functions and is expressed end-to-end in the CNS. It's been shown to play a function in pathological disorders like anxiety, persistent pain, and neurodegenerative disease [14]. The level of NPY has been observed to be lower in Alzheimer's patients. In the AD brain, NPY receptor concentrations were also shown to be lower in the temporal cortex and hippocampus. NPY will be cleaved by NEP into C-terminal fragments (CTFs), which resist the peptide’s neurotoxic to harm human neural cells. NPY ‘s property of neuroprotective in the aspect of combination between NEP may be exploited as a treatment choice for Alzheimer's disease [7].

Extra-brain factors such as CRH, angiotensin II, SST, and NPY also affect the progression of AD disease. However, it is certain that there are more intra- and extra-brain factors involved in the occurrence of AD disease and the deposition of amyloid-β. Compared with genetic mutations and other factors, external environmental factors may be better and worthier of intervention therapeutic targets. Deepening the understanding of the amyloid cascade hypothesis can help researchers develop new drugs.

4. Background of the development of related drugs

Although current medicine cannot cure Alzheimer’s disease, it can still lessen the symptoms and slow the development of memory loss and confusion. Only five medical treatments for AD have been licensed, and they all work to manage symptoms [15].

The basic function of the medicine we have is based on two ways, Cholinesterase inhibition, for example, slows AD by preventing the hydrolysis of the important neurotransmitter acetylcholine. The other is memantine (Namenda), a non-competitive N-methyl-D-aspartate (NMDA) channel blocker that lowers the action of the neurotransmitter glutamate, which binds to the NMDA receptor and plays a crucial role in learning and memory. [16] Currently, medication development research is focusing on numerous processes, including aberrant tau protein metabolism and -amyloid.

5. Proposed therapies for AD

Clinically, the conventional treatment of AD can be divided into drug treatment and non-drug treatment. For the treatment of cognitive symptoms in AD patients, drug therapy is mainly used, such as cholinesterase inhibitors, glutamate receptor antagonists, vitamin E and selegiline. Medications for the psycho-behavioral symptoms of dementia generally include cholinesterase inhibitors, antipsychotics, antidepressants, mood stabilizers, such as haloperidol, chlorpromazine, fluoxetine, lithium carbonate, carbamazepine, Diazepam, etc. This article does not elaborate on this. This article only discusses how to develop new treatments for the amyloid cascade hypothesis.

5.1 Immunotherapeutic approach

Immunotherapy is based on the immune system. It stimulates the immune cells to clear the amyloid β or generate antibodies to bind with it which can enhance the clearance of Amyloid β. Antibodies to Aβ can be utilized to prevent Alzheimer's disease by preventing A oligomerization through active or passive Aβ vaccination. This is performed by transferring the peptide from the brain to the systemic circulation with the help of microglia. Microglia are the inherent immune effector cells in the central nervous system, it mediates endogenous immune responses to central nervous system injury and disease. One medicine called aducanumab has been now proved that chronic treatment with aducanumab could inhibit toxicity and increase phagocytosis and cell viability [17].

5.2 Stem Cell Therapy

Stem cell is a class of cells that have the ability to renew themselves indefinitely, giving rise to at least one type of highly differentiated cell. As AD is the result of the apoptosis of the nerve cells, we can cure AD by replacing damaged and lost nerve cells. Stem cells can differentiate into cholinergic neurons, integrate with the host, repair neural pathways, and directly replace lost neurons, which is the main cause of neurodegenerative diseases. In 2020, a study found that Mesenchymal stem cells and their derived extracellular vesicles (MSC-EVs) have properties that protect brain neurons and prevent further degeneration [18].

5.3 Secretase inhibitors and modulators

Amyloid β is a kind of protein compound which is processed by the β-secretase and γ-secretase, so many Alzheimer's drugs have also been developed to directly target β-secretase or γ-secretase. But most of this class of inhibitors have failed in clinical trials due to poor selectivity or have difficulty in passing through the blood-brain barrier [19]. Bace-1 inhibitors are used to treat mild cognitive impairment and Alzheimer s disease. It entered phase III trial in 2016 but later the development was stopped [20].

5.4 Aβ receptor antagonist

This kind of medicine can block the pathway of Aβ, making them ineffective and thus Aβ cannot further do harm to the nerve system. TTP-488 is a kind of small molecule medicine, it can block the RAGE receptor whose interaction with Aβ can cause severe toxicity. This medicine is now in phase III trial [21].

5.5 Nonsteroidal anti-inflammatory drugs

Microglia is one of the most important immune cells in the brain, it can identify and eliminate the bad spirit in the central nervous system to maintain the environment of the system steady. However, Aβ can bind to the receptors on the surface of the microglia cells and activate them. The constant stimulation of Aβ can cause severe inflammation and the death of the nerve cells. NSAID is a kind of anti-inflammatory drug, and the trial shows that it has a good effect on inflammation in AD, the risk to get AD has a significant elimination when people use it for more than 24 months [22].

Immunotherapeutic approaches can stimulate immune cells to clear amyloid beta or produce antibodies that bind to it, thereby enhancing amyloid beta clearance. Stem cell transplantation therapy may proliferate and differentiate into lost neurons, repairing damaged nerve blocks. However, the

research on secretase inhibitors and modulators is still immature and cannot be applied to AD patients. At the same time, Aβ receptor antagonists can cause severe toxicity, and the drug is currently in phase III trials. Although Aβ plays an important role in the occurrence and development of AD, most researchers recognize its importance. However, targeting Aβ is immature at present, and new intervention methods need to be further explored in the future.

6. Conclusions

The amyloid cascade hypothesis is one of the most long-proposed and long-studied hypotheses on the pathogenesis of AD, and there are more and more in-depth insights at present. This hypothesis can be elaborated from both genetic and environmental perspectives. Genetic factors focus on the structure and function of amyloid protein-related genes, such as amyloid precursor protein gene, PSEN, and ApoE. Environmental factors mainly study the substances that affect in vivo, such as CRH, angiotensin II, SST, and NPY. So far, effective methods for relieving AD mainly include immunotherapy, which uses immune devices to remove beta-amyloid, aducanumab that can effectively reduce amyloid toxicity, and stem cell therapy replacing damaged nerve cells. As the foundation of more hypotheses, the amyloid cascade hypothesis will further promote AD-related research. More and deeper research is needed to completely overcome AD.

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