Alzheimer's Disease: Newly Proposed Pathologies and Predicted Therapies

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Abstract: Alzheimer's disease (AD) is an insidious and progressive neurodegenerative disease, and the incidence rate is generally high with the age above 70. In 2015, the number of people with dementia worldwide reached 46.8 million, and 50-75 percent were AD. The expected number of patients with AD will reach 131 million by 2050. AD can cause serious effects, including abnormal behaviors and cognitive dysfunction. The neuropathological examination can help confirm the diagnosis of early stage. However, if daily life and social functioning are significantly impaired, it will be considered as severe symptoms. In the current stage, the treatment of AD relies on traditional medications, such as donepezil and memantine. The two most indispensable mechanisms are tau protein buildup and Amyloid-beta (Aβ) deposit, which can cause neurotoxicity and cellular decay. Although people have a certain understanding of AD, the mechanisms are not optimized yet. The existing treatment methods can only try to control the development of the disease; however, the recovery of patients is continuously being studied. In this review, a comprehensive understanding of the pathology and existing treatments can help further analyze AD and investigate the future development of treatments. It introduces a general overview of pathology including the factor of aging, hippocampal alterations, and oxidative stress. Tau proteins and Aβ are also mentioned as two portions of mechanisms. Moreover, several potential treatment options have been proposed, such as anti-amyloid therapy, monoclonal antibodies, tau-targeted therapy. iPSC and CRISPR belong to two types of future treatments that are also being tested to be effective against AD.

1. Introduction

Alzheimer's disease (AD), commonly known as dementia, is a kind of chronic neurological dysfunction that occurs in the elder generation and continuously deteriorates over time. It is the main disease type of neurodegeneration. The clinical manifestations include abnormal speaking, loss of long-term memory, etc. Gradually losing the function of the body can ultimately lead to death. In general, the average survival after diagnosis is three to nine years, and less than 3% of patients survive more than 14 years after diagnosis. There are currently between 21 and 35 million people worldwide with AD. At present, China has the most AD patients around the world, the number of them reached 5.69 million in 2010. As the population ages, AD is the sixth leading cause of death in the United States. According to Alzheimer's Association's "Alzheimer's Disease Facts and Figures 2018" report, the cost of treating people with Alzheimer's disease or other dementias exceeds $250 billion ($277 billion) in the US in 2018. The total cost of AD care is expected to rise to more than $1.1 trillion by 2050. The atrophy of the brain shown as a honeycomb can be detected in patients with AD (figure 1). Clinically, AD is characterized by memory impairment, aphasia, apraxia, agnosia, impairment of visuospatial skills, executive dysfunction, personality and behavior changes, etc.

Although the concept of dementia was first proposed thousands of years ago, the clinical symptoms associated with the neurodegenerative disease were discovered by a German doctor named Aloysius "Alois" Alzheimer in 1907. He realized that his patient could recognize objects but could not store memories. After his patient died, he observed the neuritic plaques, neurofibrillary tangles, and amyloid

angiopathy in the brain. Therefore, the disease was named Alzheimer's. In the 1980s, the cognitive outcomes of the study about patients with mild dementia were found by cognitive psychology, which greatly improved the reliability of the clinical diagnosis of AD. Many studies have suggested that AD and dementing disorders have a significant effect on the cognitive function of the normal brain. At the beginning of the 21st century, a huge variety of research concentrated on the early stage of AD. The concept of mild cognitive impairment (MCI) was initially proposed by Ron Petersen and his peers. Characteristics of MCI include subjective memory complaint, relative preservation of cognition, impairing memory with aging, normal daily activities, and no symptoms of dementia. It is illustrated that the subtype of MCI "amnestic MCI" is an essential indicator of AD. In the recent decade, amyloid-beta (Aβ) and tau proteins are the two most common mechanisms of AD. Jack and his peers introduced that the accumulation of Aβ is correlated with the aggregation of tau proteins, further inducing cognitive damage [1]. Furthermore, observations of the hippocampus and cortex demonstrated alterations of brain atrophy with AD through imaging measures like magnetic resonance imaging (MRI) [2]. In this review, we will discuss how pathologies become the risk factors of AD and various treatments associated with AD.

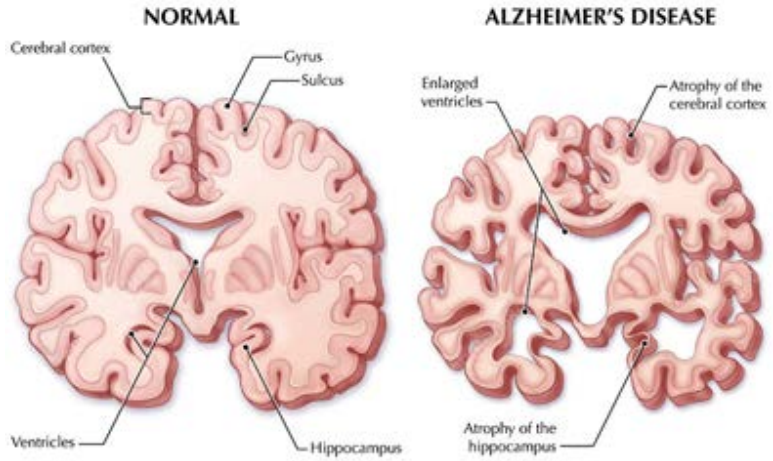

Figure 1: Comparison between normal brain and the one with AD

The left image shows the shape of a normal brain, and the right image demonstrates the brain of AD patients. Compared to normal brain, atrophy of structure appears in the brain with AD, including enlarged ventricles, atrophy of the hippocampus and the cerebral cortex. Therefore, a succession of problems induces cognitive damage.

2. Aging hippocampus and AD

In the process of dissecting a brain, the preferential measurement is the weight of the brain. A normal brain weighs between 1200 and 1400 grams; however, after the age of around 50, the brain begins to deteriorate gradually, reaching its nadir at the age of 86. According to the institute, the average human brain weighs between 1,090 and 1,100 grams at the age of 100, a significant deterioration. Upon observation, a severely atrophied brain will look like a honeycomb on the surface. Even in the absence of AD, the brain degrades with age, and the gyrus begins to shrink, leading to fewer neurons and white matter in the brain.

2.1 Hippocampus

With the gradually mature and deep research of the brain, the hippocampus catches people's attention. It is located in the temporal lobe of the brain (figure 2), with a huge variety of functions involving learning, memory consolidation, emotional expression and regulation. In the 1940s, Dr. William Beecher Scoville invited Henry Molaison to have an operation to treat epilepsy. He excided a large proportion of Molaison's temporal lobes, where the hippocampus is located. The operation was effective since the seizure frequency of epilepsy was significantly reduced, but unfortunately, people

did not realize that the removal of the hippocampus would cause severe cognitive decline. The most persuasive evidence is that Molaison was no longer able to form new memories, and the loss of memory was as serious as he could not remember whom he met within several minutes. Another research completed by scientists has observed that adult mice with damage to their hippocampus have a significantly reduced ability to recognize features in young mice. Therefore, the hippocampus of the temporal lobes is connected to cognition and memory [3]. Furthermore, the hippocampus has another function of navigation. Research has shown people who endure hippocampal damage retain the spatial behaviors of responding despite unnormal reactions. A report by Maguire indicates that an anamnestic taxi driver ambiguously pointed the relative location of landmarks in London, but successful navigation requires detailed information based on the environment.

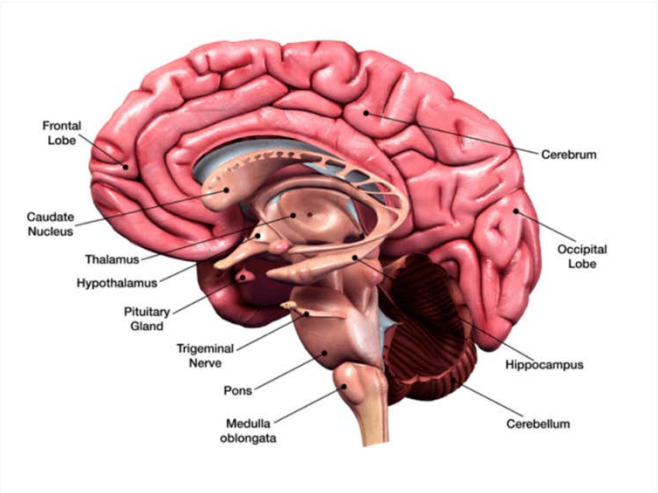

Figure 2: Human brain anatomy

The structure of the human brain includes frontal lobes, parietal lobes, occipital lobes, cerebellum, spinal cord, and temporal lobes. Among them, temporal lobes are responsible for processing emotions, the acoustic system, language, and memory. Hippocampus located in the temporal lobes has the main function of memory.

2.2 Aging Hippocampus

Aging is an essential factor that influences the alteration of the hippocampus, possibly coming with a host of problems including cognitive and social impairments, which is the evidence of neurodegenerative diseases like Alzheimer's Disease (AD). In the process of reducing neurogenesis and synaptic plasticity, increased oxidative stress and neuroinflammation are found in the aging hippocampus as well. These alterations have been linked to cognitive deficits.

(1) Volume alterations with age

The volume of the hippocampus changes with the increasing age, and the observed alterations of the gross structure and the cellular structure of the hippocampus are relevant to the decline of cognition. In an experiment completed by Driscoll in 2006, three mice groups of different ages were given memory-related tests, such as the Morris water maze and the transverse pattern learning tests. Cognitive decline was found to be particularly pronounced in older mice, and MRI has confirmed a decrease in hippocampal volume in older mice compared to younger ones. Reduced volume and activity of the hippocampus were associated with the decreased performance of episodic memory [4].

(2) Structural alterations with age

One of the reasons for the decrease in hippocampal volume is probably the loss of neurons in the brain structure. Hippocampus is comprised of the dentate gyrus (DG), cornu ammonis (CA) fields, and the subiculum (figure 3). Sub granular region (SGZ) of DG retains the ability for where neurons can be produced, and DG is the gray matter where neurons travel to the granulosa cell layer after being generated, undergoing dendritic arborization. Dendrites, a type of cellular projection, are responsible for receiving nerve impulses and transmitting them to the cell body of the neuron. Neurons are

ultimately integrated into existing neuronal circuits, thereby promoting hippocampal function. Many studies have demonstrated that most DG neurons will be replaced in adulthood. Compared to 3-month-old mice, Hippocampal neurogenic capacity in 24-month-old mice is nearly eliminated because cells are hardly to proliferate, with a reduction of 98-99% [5]. Another report demonstrates the proliferation of cells in the hippocampus has a drop of 90% in 12 months of age [6]. In addition, dendrites undergo morphological changes with increasing age, such as a reduction in the number of branches and protrusions in SGZ. That neurons stop proliferating in the hippocampus is one of the reasons inducing cognitive decline [4].

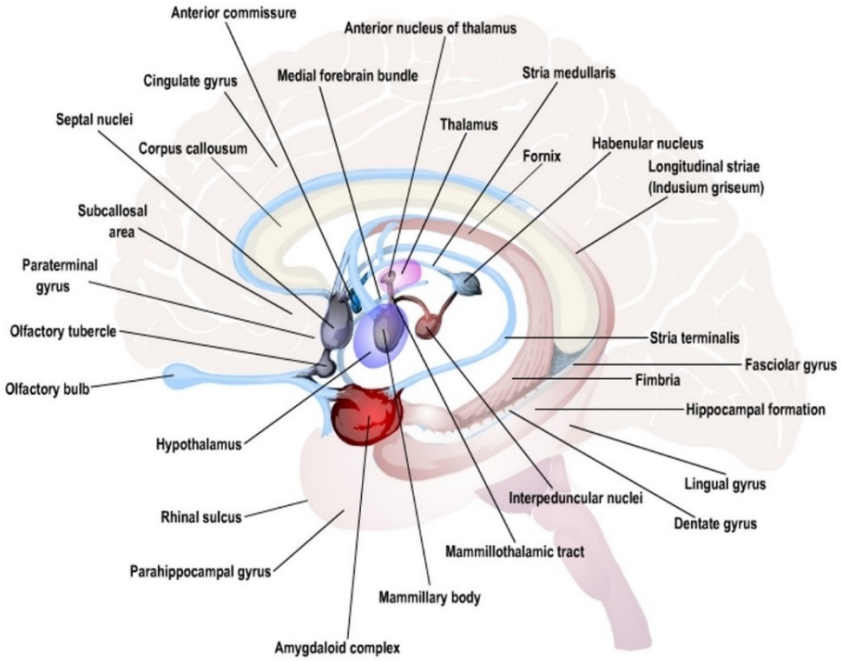

Figure 3: Structure of hippocampus

Hippocampus is comprised of pyramidal cells, and dentate gyrus (DG), subregions of cornu ammonis (CA), and the subiculum are its three main structures. DG, consisting of granule cells, is a narrow strip of gray matter where combines sensory signals contributing to form memory. The subregions of CA (CA1-CA4) are regions between DG and subiculum as an essential role of memory processing. Subiculum is an under-investigated region but also is related to memory consolidation.

(3) Vascular and inflammatory alterations with age and the leakage of BBB

The loss and dysfunction of neurons in the hippocampus are correlated with vascular inflammation. As evidence, vascular deterioration has been found in the hippocampus of 35-month-old mice [7]. Another observation demonstrates that diminished blood speed is connected to decreased neurological function in the hippocampus of rhesus [8]. Additionally, the risk of suffering from AD is threefold in patients with severe atherosclerosis [9, 10]. In the anatomy of a blood vessel with AD, the discovery of an increase in IV collagen which makes up the basement membrane, swelling in endothelial cells, and swelling of astrocyte end-feet confirm that vascular inflammation promotes the development of AD [11-15]. Pericytes are cells in the capillary walls to protect the blood-brain barrier (BBB). Vascular deterioration can damage the blood-brain barrier because of the degeneration of pericytes that induces the destruction of brain tissue. The maintenance of BBB has positive influences on basement membrane and endothelial tight junction structure and function based on pericyte-endothelial interactions [16]. Reports from several experiments demonstrate that “macromolecular permeability across the BBB in pericyte-deficient vessels occurs through a transcytosis route;” furthermore, “BBB properties are induced when the cells are in contact with astrocytes in vitro and in vivo” [17].

Of note, an experiment reported by Montagne illustrates Apolipoprotein E (APOE4), a type of gene implicated in AD, was input in the capillary pericytes in the brain of mice. This imitates a model of after capillary pericytes secrete APOE4, the cyclophilin A–matrix metalloproteinase-9 (CypA-MMP9)

pathway would be activated in the cerebrospinal fluid (CSF) so that inducing the breakdown of BBB [18]. This further results in the neurotoxic proteins entering the central nervous system, oxidative stress, and synaptic dysfunction, and thereby leads to cognitive decline.

(4) Synaptic dysfunction

Synaptic dysfunction is likely to contribute to cognitive defects because of the decreasing number of dendrites with dendritic dysfunction. Of note, by the research about the aged hippocampus, alterations of receptors (table 1) and the release of neurotransmitters have already been observed in the human brain [19, 20].

Table 1: Alterations of neurotransmitters receptors

Receptors	Alterations with AD
Cholinergic receptors	Cholinergic receptors will be activated when they bind acetylcholine that is a type of neurotransmitter, and nicotinic cholinergic receptors (NCR) and muscarinic cholinergic receptors (MCR) are two categories. The decrease of NCR in the cortex affected by AD has been proved through observing nicotine. One of the subtypes of MCR is M2, which occupies 20% of all receptors in the cortex. It has been shown a selective loss [21].
Serotonin receptors	5-HT2 receptor, which is one of the subtypes of the serotonin receptor, binds the endogenous neurotransmitter serotonin. Several studies illustrate that serotonin receptors especially 5-HT2 receptors reduce in the brain of AD patients [22].
Noradrenergic receptors	Noradrenergic receptors on nerve fibers as the entrance of neurotransmitter norepinephrine contribute to cognitive activities. Research demonstrates that pathology of AD originates at the locus coeruleus containing a huge variety of noradrenergic neurons because of reducing noradrenergic innervation [23].
Dopamine receptors	Dopamine receptors are in the central nervous system associated with stabilizing emotions [24]. The density of dopamine receptors has a decreasing trend in caudate, but it is unclear if this is relevant to AD [22].
Gamma-Aminobutyric Acid (GABA) Related receptors	GABA receptors on nerve cells receive the chemical signals for the inhibition of nerve impulses and control the excitability of neurons. A study has shown the comparison of normal and AD brains and recorded the electrophysiological activity of GABA receptors after transplanting cell membrane into Xenopus oocytes. There is a decline of GABA currents with the increasing age in AD brains, while a more obvious reduction has been found in younger AD brains. Moreover, GABA receptors in AD brains are less sensitive compared to normal brains [25].
Glutamate receptors	Synaptic glutamate receptors are glutamate-mediated to control the excitation of neurons. Decreased number of glutamate receptors has been detected in cortices; nevertheless, an increased quantity of glutamate receptors in the striatum causing denervation super sensitivity has been confirmed but without any evidence from autoradiographs [22]. The immoderate activity of N-Methyl-D-aspartate receptor (NMDAR) correlated with AD depends on glutamate availability, inducing excitotoxicity as well as cellular dysfunction [26].
Neuropeptide receptors	The neuropeptide receptor is a gateway for the entry of neuropeptides. In a mouse model with AD, an abnormally high level of neuropeptide Y has been detected in hippocampal circuits [27-29].

A synapse is a structure where a nerve impulse passes to another neuron or an effector cell. Nerve impulses are carried by electrons as the signal to transmit from the axon of the previous neuron to the cell body or dendrites of the next neuron (figure 4). In the process of the conduction of nerve impulses, Calcium ions (Ca^{2+}) enter the cytoplasm through the N-Methyl-D-aspartate receptor (NMDAR) and trigger synaptic vesicles to release stored neurotransmitters through exocytosis. Released neurotransmitters activate the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) to open the channel for electrons carried nerve signals. Eventually, nerve impulses are transmitted to another neuron [30].

The decreased amount of NMDAR correlated with neurotoxic Aβ has been shown to result in excitotoxicity caused by Ca^{2+} in nervous tissues of AD mice [31]. This will exacerbate the development of oxidative stress and imbalance of Ca^{2+} homeostasis [32], which is the state of continuously increasing concentration of Ca^{2+} and a risk factor of damaging mitochondrial function. Moreover, Soluble Aβ attaching AMPAR has been proved to influence synaptic plasticity via synaptic dysfunction and loss of dendritic spines [33].

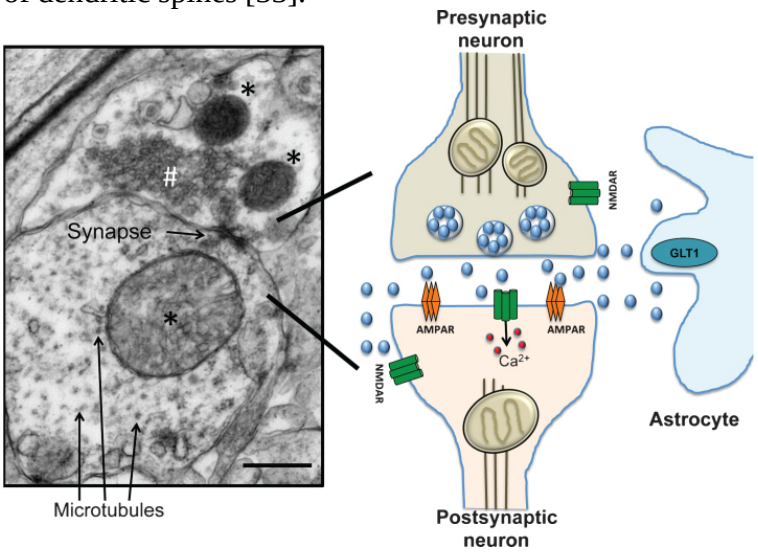

Figure 4: Structure of synapse [30]

The left image indicates the synaptic shape and features in the brain of the C57/Bl6 mouse under electron microscopy with a scale of 0.5μm (generated in Dr. Trushina's laboratory [34]). Mitochondria in presynaptic neuron and postsynaptic neurons are represented by a symbol "*", while the symbol "#" highlights the synaptic vesicles in presynaptic neurons. The right image utilizes a model to clearly illustrate the features of the synapse. Presynaptic neuron has NMDAR governing the entry of Ca^{2+}, which stimulates the synaptic vesicles to release neurotransmitters, such as the blue spheres indicated glutamate in the graph. A postsynaptic neuron contains NMDAR and AMPAR as the gateway for electrons [30].

3. Oxidative Stress

Oxidative stress, another factor correlated with AD, is described as the imbalance between anti-oxidation and overproduction of reactive oxygen species (ROS), which is an active chemical formed from oxygen (O_2). Mitochondrial dysfunction and Aβ accumulation are two of the underlying reasons for oxidative stress. Mitochondria are the organelle that is a site to generate adenosine triphosphate (ATP) and supports the production of ROS [35, 36]. Neurons in the brain, where 20% oxygen is consumed, are susceptive to oxidative stress due to high metabolic rates. Therefore, mitochondrial dysfunction will induce abnormal ROS levels with metabolic abnormality [37, 38]. The production of ROS is because of the combination of Aβ and metals during redox activity, such as copper, iron, and zinc. For instance, iron-binding with Aβ causes Fe^{3+} to become Fe^{2+} so that donating electrons to generate hydrogen peroxide (H_2O_2), which are molecules belonging to ROS. Not only Aβ contributes to ROS production in AD, but it is also suggested that Aβ boosts oxidative stress from a study of transgenic mice with presenilin-1 (PSEN 1). Rising H_2O_2 and nitric oxide (NO) levels as well as modification of proteins and lipids have been detected in the models of transgenic mice. Moreover, Aβ-binding alcohol dehydrogenase in transgenic mice stimulates the generation of ROS, exacerbating mitochondrial dysfunction [39, 40].

During the process of oxidative stress, increased concentration of reactive oxygen species (ROS) causes detected biomarkers in AD patients, including proteins such as protein carbonyls and 3-nitrotyrosine, DNA like 8-hydroxydeoxyguanosine (8-OHdG), RNA like 8-hydroxyguanosine (8-

OHG), and F2-isoprostanes (F2-IsoPs) as an example of lipids [41]. Furthermore, oxidative stress induces the elevated intercellular Ca^{2+} level, which activates a huge variety of adverse enzymes and impairs mitochondria leading to ROS production. The circumstance of numerous pathways for the entry of Ca^{2+} to neurons is defined as excitotoxicity. Therefore, excessive intercellular Ca^{2+} negatively affects cognition.

4. Mechanisms/ pathophysiology

4.1 Tau protein buildup

(1) Tau protein

One of the most universally acknowledged mechanisms of AD is the tau protein buildup. The component of the cytoskeleton includes actin filaments, microtubules, and intermediate filaments. Among them, tau protein is one of the main determinants for the stability of microtubules since binding microtubules can reduce the dissociation of tubulin molecules.

(2) Relationship between tau protein and nerve fibers in AD

With the increasing age, tau proteins in neurons possibly mutate to tau oligomerization, and tau oligomers spread to other neurons in the brain (figure 5). A soluble form of tau proteins is highly synaptic toxicity, while the soluble form can bind with the receptor, resulting in the initiation of the erosion of synapses. Hyperphosphorylation of tau proteins is one of the possibilities that trigger tau proteins to generate paired helical filaments (PHFs) because it strengthens the aggregation of tau proteins.

The combination between hyperphosphorylated tau proteins and microtubules is merely 10% of normal tau proteins, hence influencing the stabilization of binding with microtubules. This induces an abnormally elevated level of free tau protein fragments that further forms PHFs. The accumulation of PHFs constitutes neurofibrillary tangles (NFTs), which will originally appear in the entorhinal cortex and hippocampus. The abnormal alterations of tau proteins ultimately induce the dysfunction of neurons; therefore, cognitive damage is correlated with tau protein buildup [42].

(3) The process of abnormal phosphorylation of tau protein

The main causes of hyperphosphorylation include the imbalance of protein kinase and protein phosphatase. GSK-3 is a type of protein kinase including GSK-3α and GSK-3β. GSK-3β is the main kinase that catalyzes tau proteins paired phosphorylation at the PHF site, thus causing NFTs. PP-2A is the most crucial phosphatase. It has been found in the brain of AD patients that the expression levels of mRNA and proteins of phosphatase are reduced, and their activities are decreased, especially for PP-2A, which promotes the increase of tau hyperphosphorylation level.

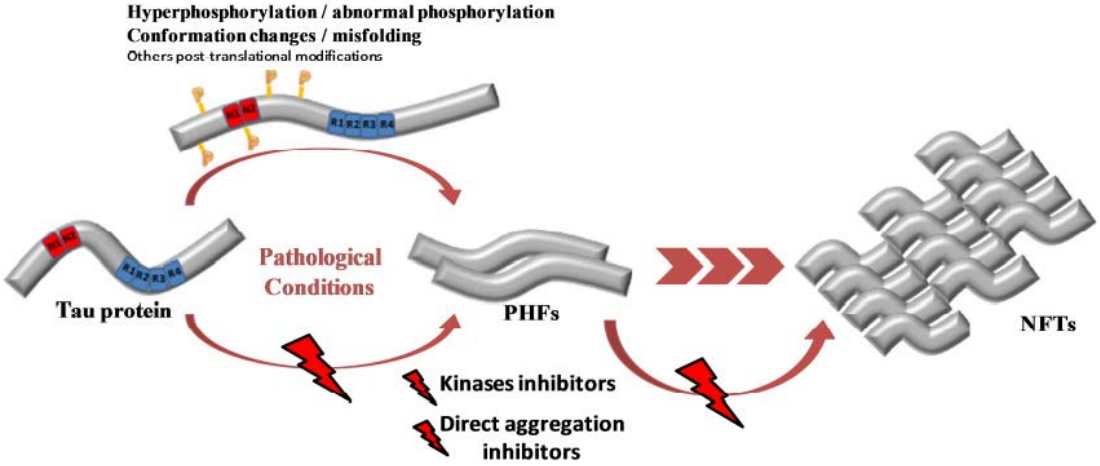

Figure 5: Process of tau protein buildup [42]

With the variation of pathological conditions such as hyperphosphorylation and abnormal phosphorylation, tau protein aggregates into the PHF structure and eventually becomes NFTs. The

accumulation of NFTs causes the damage of microtubules in the brain tissue and further results in the dysfunction of synaptic neurons leading to AD.

4.2 Amyloid beta deposit

(1) Amyloid beta

Another extensively recognized mechanism of AD is the mutation of amyloid (figure 6). It has been found that aberrant deposition of Amyloid beta (Aβ) initially appears from the decomposition of amyloid beta precursor protein (APP) in the neocortex. APP is a crucial type of membrane protein that is responsible for neural growth and repair. However, impaired APP results in a deficit of memory.

(2) Amyloid beta and AD

With age and pathological changes, the body secretes β-secretase and γ-secretase in presenilin1. Both break down APP and induce the decline of the amount of APP, resulting in the accumulation of Amyloid-β peptides (Aβ40 and Aβ42) in the central nervous system. Excessively aggregated Aβ42 forms Amyloid-β plaques. Native unfolded Aβ peptides generate oligomers via self-association [38]. These toxic oligomers can produce new oligomers and subsequently lead to the formation of aggregates. Therefore, oligomers are considered the most severe factor causing AD. The generation of protofibrils is from the self-association of the paranucleus which is produced by partially folded Aβ through hydrogen bonding and hydrophobic interactions. Protofibrils self-associate to form a fibrillar assembly. Overall, Aβ peptides are the main factor, causing tau pathological induction and neurotoxicity, further leading to neuronal cell death and neurodegeneration [43].

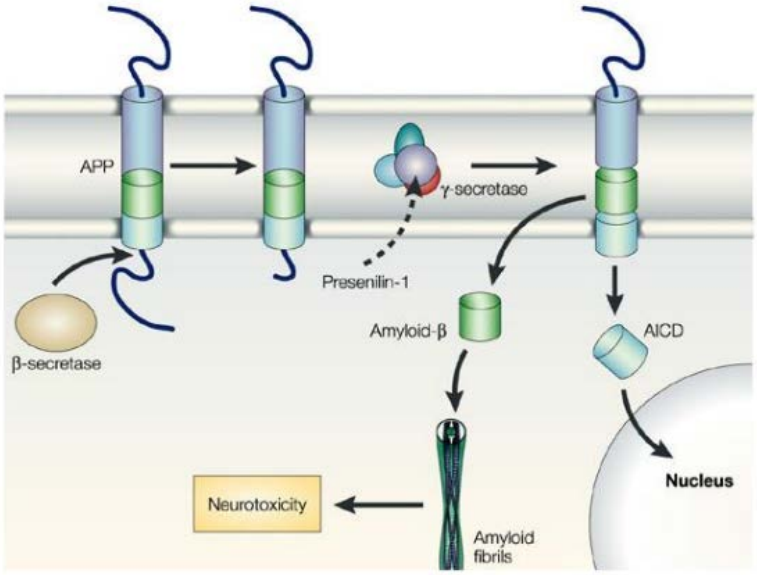

Figure 6: Process of the formation of amyloid fibrils [43]

APP is decomposed to Aβ with the secretion of β-secretase and γ-secretase in presenilin1. Partially folded Aβ peptides undergo self-association to generate protofibrils, which accumulate to produce long fibrillar aggregates. This indicates the pathology of neurotoxicity in AD patients.

5. Therapy

AD has seriously affected people's lives, especially for the elder generation. A huge variety of evidence from clinical trials indicates a 0.4% success rate for medications that are available to change the development of AD in patients. Therefore, current medications (table 2) are only accessible to the control of symptoms [44].

Table 2-1: Current medications

Current drug treatment	Related content of medications
Cholinesterase inhibitors	The function of cholinesterase inhibitors includes the prevention of the decomposition of acetylcholine, which is one of the neurotransmitters playing a role in the communication between nerve cells. Reduction of nerve cell activity has been detected in severe AD patients, and the target of utilizing cholinesterase inhibitors is to promote the communication and signal transmission between nerve cells [45]. Donepezil is the most extensively used medication which is initially prescribed at a dose of 5mg in the evening after a month increased to 10mg if there is no obvious side effect. However, near one-third of people hardly tolerate the side effects of cholinesterase inhibitors, including gastrointestinal, fatigue and muscle cramps, and skin redness and itching [44].
Memantine	Memantine can halt the NMDA receptor in order to reduce the risk of neuron loss and repair impaired neurons, thereby improving symptoms. Memantine is prescribed at an initial dose of 5 mg daily, increasing weekly by 5 mg to a maximum dose of 20 mg. Compared to cholinesterase inhibitors, utilizing memantine has minor side effects. However, there are still side effects that will occur such as headache, dizziness, somnolence, constipation, and hypertension. Studies have proved that memantine is an efficient agent for the moderation of severe AD [44].

Table 2-2: Possible future drug treatment

Potential future drug treatment	Related content of strategies
Anti-amyloid therapy	The target of anti-amyloid therapy is to inhibit the formation of Aβ oligomerization and further prevent cerebral amyloidogenesis. Aβ can bind zinc ion in its metal-binding domain (Aβ1-16) [46, 47] where provides motifs for Aβ dimerization to increase the stability of assembling Aβ [48]. Targeted restriction of the motif can moderate zinc-induced Aβ oligomerization, which is possibly triggered by the formation of zinc-dependent heterodimers via motifs, thereby preventing cerebral amyloidogenesis [49].
Monoclonal antibodies	Toxic amyloid-β species can be eliminated through microglia activated by monoclonal antibodies (mAbs), which is a type of passive immunization. This strategy can terminate the accumulation of Aβ peptides, thereby managing the decline of cognition. However, bapineuzumab and solanezumab as two experimental projects are unsuccessful to give an expected result because of wrong targeting of Aβ species or an inappropriate period of disease [50].
Tau-targeted therapy	Tau proteins are responsible for the stability of microtubules by combining them. Hyperphosphorylated tau proteins affect the stability of microtubules and further lead to AD. Therefore, tau-targeted therapy is to prevent hyperphosphorylation as well as stabilize microtubules [44]. Current clinical medications include active and passive immunotherapies, phosphatase activators, microtubule stabilizers [51]. Active immunotherapy is to set an immune response against disease; passive immunotherapy is to give immune molecules for patients who cannot produce them. Phosphatase activators stimulate the body to secrete phosphatase which can remove phosphate to inhibit hyperphosphorylation. Microtubule stabilizers are agents to promote the aggregation of purified tubulin and increase the density of microtubules.

6. Future orientation

6.1 iPSCs Treatment:

(1) Introduction of induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) refer to the reprogramming of terminally differentiated somatic cells into pluripotent stem cells by introducing specific transcription factors. Differentiated

cells can recover to totipotency so that can form embryonic stem cell lines, or further develop into new individuals. iPSCs technology can be used to make stem cells by taking cells from patients. Therefore, there is no problem with immune rejection. iPSCs have been successfully reprogrammed in other neurodegenerative diseases including Parkinson's disease, Huntington's disease, etc. Therefore, the therapy of reprogramming iPSCs is one of the most promising strategies to treat AD at present [52].

(2) iPSCs treatment and AD

iPSCs can be differentiated into human neural cells so that repair the loss of neurons in the brain structure. Astrocytes supply nutrition, energy, and metabolic support to neurons and other cells in the brain [53, 54]. They are correlated with neurons and synapses because they regulate the excitability of neurons by controlling neurotransmitters like glutamate [55, 56]. Astrocytes can be differentiated from gliospheres and the reprogramming of fibroblast cells [52]. That co-cultural human neurons survive and mature can be facilitated by iPSC-derived astrocytes based on the result of research [57].

6.2 CRISPR gene editing:

(1) Introduction of CRISPR gene editing

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a brand-new technology to cut dysfunctional DNA by Cas9 enzyme to treat gene-related disease. Guide RNA is responsible for guiding Cas9 enzyme to provide the correct position of DNA to cut because guide RNA can only bind to targeting DNA instead of other DNA strands. Natural DNA has the function to repair DNA strands eliminated by Cas9 enzyme. This strategy is effective, accurate, and capable of controlling the heredity of dysfunctional genes. Moreover, unlike medications, CRISPR is more accessible to patients if disposed appropriately because side effects are reduced to a large extent.

(2) CRISPR and AD

AD can be divided into familial AD (FAD) and sporadic AD (SAD). Patients with FAD through inherited genes like presenilin (PSEN 1 and PSEN 2) and amyloid precursor protein (APP) only occupy less than 1% in total AD cases. Mutations of PSEN 1 and PSEN 2 can speed up the generation of Aβ so that result in early AD onset, which refers to the age of patients being less than 60. The utilization of CRISPR can eliminate the mutated PSEN gene in FAD. The majority of AD cases is SAD, and Apolipoprotein E (APOE) gene is responsible for SAD. People carrying a single copy of APOE4 have 2-3 times more incidence of AD than people who carry APOE2 or APOE3. APOE4 can stimulate the production of phosphorylated tau proteins in neurons derived from iPSCs as well [58, 59]. Therefore, CRISPR as a gene-editing method can convert APOE4 to APOE3 or APOE2, further reducing the incidence of AD [60].

7. Conclusion

In the review, we concentrated on the pathology of AD, including the aging hippocampus, leakage of BBB, and oxidative stress. Cognitive deficits and memory decline occur when the hippocampus is damaged, and BBB leakage caused by APOE4 and oxidative stress are two of the new proposed pathologies. Accumulation of Aβ can form amyloid fibrils that have neurotoxicity; tau proteins aggregate to constitute NFTs which can induce neuronal dysfunction. Current medications are based on the control of pathology, and potential strategies are undergoing clinical trials. iPSCs can be differentiated as neuronal cells to repair brain structure, but the derived cells still carry the genes which possibly lead to Aβ aggregate or other crucial factors of AD. Therefore, iPSCs are proposed to be utilized with CRISPR which can eliminate genes correlated with AD. In the future, AD will be completely treated by modifying genes with fewer side effects, and the likelihood of inheritance will be reduced.

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