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Mechanism and treatment of Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is a type of neurodegenerative disease that affects the nerves and tends to develop slowly, with symptoms worsening over time. It is responsible for causing 60 to 70% of cases of dementia, and it is becoming increasingly common. Currently, around 50 million people worldwide are affected, with the majority being over the age of 65. Despite the many experimental studies and cases, no treatment has been found that can prevent or reverse the progression of AD, and only a few methods are available that can temporarily alleviate symptoms. At present, the main focus of treatment is still on managing symptoms, although efforts are being made to reduce the production and impact of brain pathology. This article provides an overview of AD and its underlying causes, as well as current treatment options and possible future treatments that are undergoing testing. This article also discusses potential directions and predictions for new treatments that may be effective against AD.

Keywords: AD, pathogenesis, treatment.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease and is often accompanied by many symptoms including deficits of new memory storage in the initial stages and a progressive decline in cognitive ability in the later [1]. This disease is first described by Alois Alzheimer in 1906, and two main pathological processes known as the deposition of tau and amyloid beta protein have been discovered during this over a century's related research [1]. However, though the understanding of AD pathogenesis stages further and many hypotheses have been put forward, there are still no efficient drugs that can alter the course of the disease. There are two current classes of drugs only, which are memantine and cholinesterase inhibitors and they simply act to control the symptom.

This review will overview the AD pathogenesis, summarize current pharmacological treatment, and highlight potential future therapies based on main mechanisms.

2. Pathogenesis

2.1. Mechanisms of apoptosis and pyroptosis

Apoptosis is a type of programmed death that exists throughout the life of multicellular organisms and can timely remove superfluous or damaged cells from the body. Currently known pathways that can

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mediate apoptosis include: the death receptor activation pathway, mitochondrial damage pathway, B granzyme signalling pathway, endoplasmic reticulum stress pathway and so on. Apoptosis is a pathophysiological stimulatory signal of the cell to the environment and is also a death process. In this process, cell contraction, chromatin condensation, nuclear segmentation, and finally cell decomposition into discrete membrane-bound apoptotic bodies will occur [2]. The induction of extracellular stimuli is crucial for cell apotosis.

2.1.1. Mitochondrial damage pathway. Apoptosis is initiated by the activation of the mitochondrial apoptotic pathway in response to internal apoptotic stimuli. This process is regulated by Bcl-2 proteins, and permeabilization of the outer mitochondrial motif leads to the incorporation of cytochrome c into the cytoplasm. A binding site for the adaptor protein Apaf-1 is present on the cytochrome c molecule, which, in response to ATP, combines with the 7-adaptor protein Apaf-1 in the cytosol, allowing it to undergo allosteric effects and become activated. Activated Apaf-1 aggregates and activates caspase-9 in a crad-crad manner to form apoptotic bodies composed of cytochrome c and others. Caspase-7, which is subject to this cleavage and becomes activated, causes downstream protein degradation related to cell life, ultimately causing apoptosis. Or apoptosis can also be mediated through the AIF protein. AIF can be released from mitochondria to the cytosol when cells are subjected to internal apoptotic stimuli and enters the nucleus and damages DNA, leading to cell death. In this process, bel-2-mediated MOMP is involved in the translocation of AIF from the inner mitochondrial to the cytosol [3].

2.1.2. Death receptor activation pathways. TNF receptors undergo oligomerization and structural changes by binding to associated ligands, exposing a DD capable of binding to adaptor proteins. When activated, adaptor proteins trigger the activation of downstream caspases, leading to apoptosis. Among them, Fas is the most studied death ligand. Its activation occurs by trimerization upon binding to the ligand FasL, and activated Fas can bind to and aggregate the Fas-associated death domain FADD through its DD, resulting in a change in the conformation of FADD. Whereas this change can lead to the activation of caspase-8, forming a protein complex (similar to the apoptosome) consisting of FasL, Fas, FADD, and Caspase-8, which can activate Caspase-3, triggering the cascade of apoptosis [3].

2.1.3. B Granzyme signaling pathway. Natural killer cells, like cytotoxic T cells, and lymphokine-activated killer cells, can induce apoptosis of target cells. FasL expressed on the surface of these cells binds FAS, and activates apoptotic pathways outside the target cells. Such toxic lymphocytes also deliver toxic particles to target cells, such as TNF, Granzyme B, and others. Perforin forms intermembrane channels on the target cell surface, facilitating the transfer of B granzyme to the interior of the target cell. Granzyme B has a proteolytic effect, it will cleave and activate caspases, and proceed apoptosis. Granzyme B mediates apoptotic effects more rapidly than direct activation of caspases by BH3-only proteins [3].

2.2. Endoplasmic reticulum stress pathway

The response of cells to endoplasmic reticulum stress is protective in nature. To prevent the accumulation of unfolded protein, the cells lower their concentration and inhibit the clumping of these proteins. When the endoplasmic reticulum becomes overloaded with misfolded proteins and there is a disturbance in calcium homeostasis, cells initiate various signaling pathways like unfolded protein response, endoplasmic reticulum overload reaction, and caspase-12 mediated apoptosis pathway as a reaction process. The ER stress induces the expression of glucose regulatory proteins GRP78 and GRP94 as endoplasmic reticulum molecular partners, leading to protective effects. However, it can also independently trigger cell apoptosis, impacting how the stress cells adapt, get injured, or undergo apoptosis in the long run.

Pathologically, Alzheimer's disease (AD) is characterized by the accumulation of hyperphosphorylated tau proteins to form Neurofibrillary tangles (NFTs) and the overproduction, oligopolization and deposition of β-amyloid (Aβ) of outside cells in the brain, resulting in a gradual

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decline in cognitive function and the eventual onset of dementia [4]. NFTs of hyperphosphorylated tau proteins and amyloid plaques of insoluble Aβ peptides are seen on histopathological examination in AD. The accumulation of these abnormal proteins in the brain leads to neuroinflammation, glial cell activation and ultimately neurodegeneration. AD is associated with various disturbances in the molecular mechanism, resulting in ER stress. One such disturbance involves the aggregation of peptides, which can obstruct NMDA-R and trigger the entry of calcium into the cytoplasm. Disturbances in the amounts of the inositol-1,4,5-trisphosphate receptor (IP3-R) and ryanodine receptor (RyR) channels can cause disruptions in proper calcium regulation which can ultimately result in the demise of cells via the mitochondrial apoptotic pathway. The aggregate impact of these various cellular occurrences gives rise to long-standing ER stress [5]. The gradual accumulation and aggregation of hyperphosphorylated tau proteins or A peptides in AD cause irreversible ER stress, leading to synaptic dysfunction and ultimately, neurodegeneration.

The onset of AD is linked to the buildup of incorrectly shaped proteins in affected neurons, abnormalities in metabolism, heightened levels of oxidative stress, and a type of neuroinflammation that involves the glial cells in close proximity to these damaged neurons, including microglia and astrocytes. In this case, homeostasis is inhibited in the emergency room [4]. Thus, the AD brain exhibits ER stress.

2.3. The correlation between cell apoptosis and AD

Nowadays apoptotic mechanisms have been clearly demonstrated to play a major role in the pathogenesis of AD. Its process includes β- Amyloid aggregates and triggers apoptosis by inducing cellular early immediate response genes and their expression (c-fos, c-myc) by oxygen radicals. Oxidative stress has a great degree of correlation with it, and also studies have shown that oxidative free radicals are able to directly trigger the apoptotic mechanism and cause neuronal apoptosis [6].

2.4. Mechanisms of autophagy lysosomal pathway and ubiquitination proteasome system

Autophagy lysosomal pathway (ALP) and ubiquitination proteasome system (UPS) are related to AD or other neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease (HD), and prion disease.

Both ALP and UPS are crucial for the maintenance of cellular homeostasis by degrading and recycling cellular components to avoid waste. They both serve the same purpose: degrade the large protein complex into short peptides to be recycled and uptake by the cell for the synthesis of other proteins. They both experience the ubiquitination process, in which the substrate protein can be cascade marked with linear ubiquitin by three enzymes including E1, E2, and E3 as the target of degradation through the covalent combination with the ubiquitin molecule. As a result, the protein will be recognized by the 26S proteasome complex and be degraded.

In UPS, mono ubiquitin or polyubiquitin (Lys 11, 48) induces the target in the E3 stage. It uses proteasomes to degrade protein molecules. The proteasome is a combination of alpha and beta subunits in the beginning. It can switch to a 26S style with the help of ATP. The newly added 19S regulatory subunit can be functional in ubiquitin removal, the reorganization of substances, and the facilitation of protein unfolding. The unfolded protein will then be attached to the proteolytic site for degradation and the protein will be degraded into smaller peptides there. This process is also related to the cell cycle. It functions in degrading proteins responsible for pushing the cell into the next checkpoint. It also plays a role in antigen presentation. Intracellular proteins can be degraded into smaller peptides and presented onto the surface of the cell through this pathway.

The aggregation of insoluble protein in the brain nerve cells is a common symptom in AD and several other chronic neurodegenerative diseases. This aggregation could be due to the dysfunction or overburden of the UPS, or from structural or functional changes in the protein [7]. These two kinds of causes can disturb the normal recognition and degradation of protein by the UPS. The UPS takes part in maintaining the normal functions of synapses, so it is common that synaptic dysfunction is observed in AD since the deposition of insoluble protein aggregates in the brain of AD patients could defective proteolysis.

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In ALP, polyubiquitin (Lys 48, 63) induces the target into ALP in the E3 stage. This autophagy-lysosome pathway is often responsible for those that cannot be easily targeted to the proteasome, such as larger protein aggregates, large organelles such as mitochondria, or more complex structures which may inhibit the association of proteasome onto these components. ALP often involves in the formation of a double membrane vesicle known as an autophagosome. It forms around the cellular component that needs to be degraded. Lysosomes then degraded the contents in autophagosomes into amino acids and fatty acids which can be recycled by the cell. This process is regulated tightly by complex protein networks and signal pathways including the AMPK pathway. It contains three different types, macroautophagy, chaperone-mediated autophagy, and microautophagy.

ALP involves in the degradation of proteins. The deficits in the ALP will lead to the aggregate of proteins, the generation of toxic protein species, and the accumulation of dysfunctional organelles, which are commonly witnessed in AD, PD, HD, and prion disease [8].

3. Treatment

3.1. Current treatments

Presently, there is no cure for AD and there are only some symptomatic treatments, most of which are moderate. The current treatment can be divided into two types: drug therapy and psychotherapy.

There are five drugs commonly used to improve cognitive impairment in AD, four of which are acetylcholinesterase inhibitors, and the other is an NMDA receptor antagonist.

In AD, the activity of choline neurons is reduced, resulting in a decline in acetylcholine concentration between synapses. To counteract this, acetylcholine esterase inhibitors can slow down the degradation rate of acetylcholine, which increases its concentration [9]. The first generation of cholinesterase inhibitors, Tacrine, had limited use due to hepatotoxicity [10]. Later on, Donepezil, Rivastigmine, and Galantamine were introduced and found to be effective in controlling the symptoms of mild and moderate AD, and there is evidence that they work for severe patients as well. However, these drugs do not delay the occurrence of AD in patients with mild intellectual disabilities. An excessive amount of choline can cause nausea and vomiting, which are the most frequently encountered side effects of these medications. Muscle cramps, bradycardia, reduced appetite and weight, and heightened production of gastric acid are among the less frequent side effects [11]. About 10% to 20% of patients may experience side effects that range from mild to moderate severity.

By non-competitively inhibiting NMDA receptors, memantine can prevent the loss of neurons and facilitate the functional recovery of damaged neurons, thus providing neuroprotection and improving symptoms. Its effectiveness has been demonstrated in moderate to severe AD, while its efficacy in mild AD remains unsupported. Moreover, the addition of memantine to polyperzane monotherapy may benefit individuals with mid-stage AD or cognitive impairment [9].

However, the efficacy of these drugs is not great, and so far, there is no evidence that these drugs can delay or stop the source of the disease.

Alternative therapies chosen by patients may include the use of the nutraceutical huperzine A, which is believed to improve memory function and daily activities. However, it is important to consider that its potency and purity may vary. It has been identified that a deficiency in vitamin D may increase the risk of developing dementia, and thus, patients who have been diagnosed with a deficiency are recommended to supplement an appropriate amount of vitamin D [12]. Adjuvant drug therapy, such as social psychotherapy, can be used to complement traditional drug therapy [11]. Social psychotherapy involves various interventional methods, including behavioural, emotional, cognitive, and stimulating therapies. Behavioural therapy aims to reduce specific symptoms by identifying the cause and effect of problematic behaviour. Emotional-oriented therapy includes several methods, but there is no conclusive evidence supporting their effectiveness. Cognitive-oriented therapy involves re-training patients to improve their mental functioning and restore reality orientation. Stimulation-oriented treatments, such as those involving art, music, pets, sports, or other recreational activities, may improve a patient's

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behaviour, mood, and functions, although the efficacy of non-invasive and invasive brain stimulation on AD remains unclear.

Compared with people who do not exercise regularly, less atrophy is observed in the brains of patients with AD genetic risk factors, indicating that aerobic activity can prevent neurodegeneration [13]. Regular aerobic exercise can prevent metabolic diseases such as diabetes and also shows the maintenance of the body function of AD patients. As patients age, physical exercise can not only prevent the reduction or loss of strength and agility but also reduce neuropsychiatric symptoms and the care requirements associated with these problems [12].

3.2. Future treatment directions for AD

There is still great room for improvement in the medical direction of treating AD. The following are several currently popular and promising future methods for treating AD.

3.2.1. Therapeutic approaches related to traditional Chinese medicine for AD. With the improvement of the global medical level, the ageing of the population has gradually intensified, and the incidence rate of AD has increased significantly. At present, the global medical level has not reached the level of developing specific drugs to treat AD, and can only delay the course of the disease at most. One of the new treatment methods provides a good idea for the future treatment of AD, which is traditional Chinese medicine treatment. Traditional Chinese medicine has the advantages of stable therapeutic effects, low toxicity, multiple targets, multiple pathways, and multiple systems in improving AD symptoms [14].

From the aspect of TCM Pathology, AD is dominated by the loss of seminal oligo myelination and deficiency of Qi and blood, so there are methods for toning the spleen and stomach and kidneys. The spleen and kidney as the source of breath, blood biochemistry, and fine encapsulation, play an important role in solid fundamental, machine regulation. In traditional Chinese medicine (TCM), the treatment of ad is based on the spleen stomach and kidneys, and the most common formulas used clinically are qifuyin and Huanshaodan. Panax ginseng, Atractylodes macrocephala, and Glycyrrhiza consumed by Qi Fu are beneficial for robust spleen and stomach, staghorn gum, balanc gum, and acanthose gum can add refined Qi, and cooked Rehmannia is used for tonic intestine. Poria cocos, Z. jujuba, Chinese yam, Lycium barbarum etc. in also shaodan can gentle the body balance [14]. In response to this therapy, a well-known Chinese patent medicine, named ginseng Yang Rong decoction, was screened for experiments with mice as research samples. It was found that the decoction effectively improved spatial learning and memory ability, attenuated oxidative stress and hippocampal tissue damage in mice, increased ACh level in brain tissue, reduced AChE activity, and upregulated the protein expression of PSD95 and NR2B [15].

3.2.2. Insulin regulation is associated with future AD treatment. It has been observed that diabetes has the function of inducing AD pathogenesis. Mellitus generally results from inadequate insulin secretion. Its implication in AD is seen with insulin acting as a neuromodulator in the brain. Insulin dysregulation may contribute to AD pathology through several mechanisms, including reduced cortical glucose utilization. In addition to this, advanced glycation end products will increase oxidative stress, tau phosphorylation, and neurofibrillary tangles; While inhibition of insulin-degrading enzymes- increases β- Amyloid aggregation. Insulin and glucose regulation may emerge as future AD treatment options [16].

3.2.3. ALP. A major regulator of ALP is transcription factor EB (TFEB). This is a key factor in coordinating autophagy by regulating the formation of autophagosome and the fusion of autophagosome-lysosome positively through a selective combination with a promoter element called CLEAR [17, 18]. It also enhances cellular clearance through lysosomal exocytosis. It regulates metabolism and cellular clearance through lysosomal adaptation.

It has been verified that in multiple mouse models of AD for both Aβ and tau pathology, there is a beneficial effect mediated by TFEB.

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For tau, through a TFEB–PTEN–Akt–mTOR–TFEB feedback regulatory loop, TFEB is further activated by the upregulation of PTEN and inhibition of Akt and mTOR induced by TFEB. As a result, the exogenous TFEB expression can enhance the ALP, and reduce tau pathology. For amyloid pathology, Aβ plaque pathology in the APP/PS1 mouse model can be reduced by a mechanism of astrocyte uptake and lysosomal degradation of Aβ, through TFEB expression in astrocytes [17].

There are many current treatments including Celastrol and a novel curcumin analogue C1, which are two kinds of TFEB agonists, and three-needle Electroacupuncture ameliorates (TNEA), which can be used to activate TFEB [18-20].

In summary, drugs that focus on TFEB might have a positive effect on AD and many treatments had put forward through this.

3.2.4. UPS. E3s mainly determine the specificity of substrates, so they are the best potential therapeutic targets among the enzymes that are responsible for combining ubiquitin with substrates.

Modulating the specific DUBs to enhance the deubiquitylation of polyubiquitin chains of mutant UBB+1, which inhibits proteasomes in the AD brain is another possibility.

Activation of the proteasome can also be an area of new drugs. It is a feature in AD patients that abnormal proteins aggregate or proteasomes inhibit. It could be efficient to remove the aggregated proteins or organelles that accumulate in the brain by enhancing proteasome activity in the following ways: by up-regulating the 19S and 20S complexes' assembly to increase the activity of the proteasome; by promoting the recognition of ubiquitylated proteins in protein aggregates; by modulating the chaperone or ATPase activity to unfold the aggregated proteins and by stimulating the catalytic activity of the proteasome [21].

In summary, drugs that focus on Ubiquitin-conjugating enzymes, DUBs and the proteasome might also have a positive effect on AD.

4. Conclusion

After collated studies of endoplasmic reticulum stress mechanisms, apoptosis and pyroptosis mechanisms, autophagy-lysosome pathway, and ubiquitination proteasome system mechanisms, all found their inseparable association with AD pathogenesis. This also drives further thoughts and actions on the treatment of AD. Existing pharmacological or psychological treatment modalities for ad including acetylcholinesterase inhibitors and NMDA receptor antagonists have nevertheless played a role in improving cognition in AD patients. The areas of TCM pharmacy, insulin mediation, ALP, and UPS that are mentioned will provide new ideas for both AD treatment and drug development for the future. And all the above treatment modalities are closely related to the mechanisms that lead to the pathogenesis of AD and play a regulatory role. It is believed that in the future, people's research on AD and the research and development of drugs will be further.

5. Authors' contribution

All the authors contributed equally and their names were listed in alphabetical order.

References

[1] Soria Lopez JA, González HM, Léger GC. Alzheimer's disease. Handb Clin Neurol. 2019; 167:231-255.

[2] Ding S P, Wang G F, Wu L X. Mechanisms of mycobacteria induced apoptosis in host immune cells. Chinese Journal of Pathogenic Biology. 17(12):1480-1483.

[3] Li M, Lin J. 2014. Apoptotic pathways and their mechanisms. International Journal of Obstetrics and Gynecology. 41(2):103-107.

[4] Ajoolabady A, Lindholm D, Ren J, Pratico D. ER stress and UPR in AD: mechanisms, pathogenesis, treatments. Cell Death Dis. 2022 Aug 15;13(8):706.

[5] Gerakis Y, Hetz C. Emerging roles of ER stress in the etiology and pathogenesis of AD. FEBS J. 2018 Mar;285(6):995-1011.

[6] Xu C Q, Qian C Y. 1996. Apoptosis and AD. International Register of medical gerontology. 17(6):241-243.
[7] Upadhya SC, Hegde AN. Role of the ubiquitin-proteasome system in AD. BMC Biochem. 2007 Nov 22;8 Suppl 1(Suppl 1):S12.
[8] Zhang Y, Chen X, Zhao Y, Ponnusamy M, Liu Y. The role of ubiquitin proteasomal system and autophagy-lysosome pathway in AD. Rev Neurosci. 2017 Nov 27;28(8):861-868.
[9] Cunnane S.C., Chouinard-Watkins R., Castellano C.A., and Bar- berger-Gateau P., 2013, Docosahexaenoic acid homeosta- sis, brain aging and AD: can we reconcile the evidence? Prostaglandins Leukot. Essent. Fatty Acids, 88(1): 61-70.
[10] Briggs R, Kennelly SP, O'Neill D. Drug treatments in AD. Clin Med (Lond). 2016 Jun;16(3):247-53. doi: 10.7861/clinmedicine.16-3-247.
[11] Xu Hui. Prevention, clinical treatment and nursing of AD [J]. Genomics and Applied Biology, 2021,40(03):1430-1434.
[12] Weller J, Budson A. Current understanding of AD diagnosis and treatment. F1000Res. 2018 Jul 31;7:F1000 Faculty Rev-1161. doi: 10.12688/f1000research.14506.1. PMID: 30135715; PMCID: PMC6073093.
[13] Smith JC, Nielson KA, Woodard JL, et al.: Physical activity reduces hippocampal atrophy in elders at genetic risk for AD.
[14] Huang Z H, Fang Y, Yu Q, Wang X Q, Xu X T, Wang T. 2022. Exploring the pathogenesis and treatment of AD based on the concept of unity of form and spirit. Forum on Traditional Chinese Medicine. 37(5):16-18.
[15] Lv X, Jiang M M, Zhu M Y, Yuan H Y, Guo Z H, W Y, Gong Y S. 2022. Effects of Panax ginseng Yanrong Decoction on improving learning and memory impairment in AD mice. Chinese patent drug. 44(12):3823-3829
[16] Hillel G. 2023. Journal | [J] Central nervous system spectrum. Will diabetes protect or cause AD? Deep understanding of the pathobiology and future treatment of AD. Journal | [J] Central nervous system spectrum. 8(11):815-822.
[17] Martini-Stoica H, Xu Y, Ballabio A, Zheng H. The Autophagy-Lysosomal Pathway in Neurodegeneration: A TFEB Perspective. Trends Neurosci. 2016 Apr;39(4):221-234.
[18] Zheng X, Lin W, Jiang Y, Lu K, Wei W, Huo Q, Cui S, Yang X, Li M, Xu N, Tang C, Song JX. Electroacupuncture ameliorates beta-amyloid pathology and cognitive impairment in AD via a novel mechanism involving the activation of TFEB (transcription factor EB). Autophagy. 2021 Nov;17(11):3833-3847.
[19] Song JX, Malampati S, Zeng Y, Durairajan SSK, Yang CB, Tong BC, Iyaswamy A, Shang WB, Sreenivasmurthy SG, Zhu Z, Cheung KH, Lu JH, Tang C, Xu N, Li M. A small molecule transcription factor EB activator ameliorates beta-amyloid precursor protein and Tau pathology in AD models. Aging Cell. 2020 Feb;19(2):e13069.
[20] Zhang W, Wang J, Yang C. Celastrol, a TFEB (transcription factor EB) agonist, is a promising drug candidate for AD. Autophagy. 2022 Jul;18(7):1740-1742.
[21] Upadhya SC, Hegde AN. Role of the ubiquitin-proteasome system in AD. BMC Biochem. 2007 Nov 22;8 Suppl 1(Suppl 1):S12.