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A review of the pathophysiology of Alzheimer disease and their therapeutic strategies

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ABSTRACT

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder causing dementia in older adults, characterized by progressive brain degeneration that occurs across all clinical stages.Key features of Alzheimer's disease include the loss of neurons and synapses in targeted areas of the brain, including cerebral cortex and subcortical areas, leading to characteristic cognitive decline. The development of these AD markers is linked to a number of mechanisms, including apolipoprotein E, the mechanism of amyloid B processes leading to the neurodegenerative processions, protein Tau, and the cholinergic hypothesis. Genetic imprint factors are also considered familial legacy. Although there isn't a cure for AD, there are medication therapies that can help with a number of its symptoms. Amyloid β and protein Tau-targeting therapies are two examples of therapeutic approaches that concentrate on specific cellular pathways that can cause Alzheimer's disease. However, research is still ongoing to alleviate the symptoms of the disease or try to control it.

Keywords: *Alzheimer, Amyloid B, Neurodegenerative, Oxidative stress, Treatment*

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia in older adults, marked by progressive neurodegenerative alterations that affect the brain across different stages of the disease [1]. Neuronal and synaptic degeneration in the cerebral cortex and specific subcortical regions is a hallmark of AD, leading to pronounced atrophy in regions such ascingulate gyrus, frontal cortex, parietal lobe, and temporal lobe[2].The amygdalaand hippocampus that locate within the medial temporal lobe, are heavily impacted in this neurodegenerative disorder,they are initial sites where neurodegeneration occurs[3].Alzheimer's disease typically affects the hippocampus early on, leading to initial symptoms that include memory loss and disorientation due to the damage in this critical brain region[2].The amygdala, another key structure in the temporal lobe, also undergoes atrophy in Alzheimer's disease, although at a rate that is either comparable to or less important than the hippocampus [3]. Thus, AD is characterized as a central nervous system disorder marked by progressive neuronal decline, leading to cognitive impairment, memory loss, and disruptions in daily activities[4].Oxidative stress occurs when there's an imbalance between antioxidants and pro-oxidants, with pro-oxidants gaining the upper hand[5]. Antioxidants play a major role in protecting against molecular oxidativedamage[6]. Indeed Alzheimer's disease exposes too many complications that can be related to oxidative stress that is also associated with the appearance of several pathologies[7]. Our review aimed to focus on understanding Alzheimer's disease pathophysiology and exploring strategies for treatment and prevention.

2. Research Methodology

This review gathered, examined, and summarized the literature on Alzheimer's diseasepathophysiology, mechanism of disease, and treatment mechanism. A comprehensive search was conducted using prominent scientific databases, including ScienceDirect, PubMed, Web of Science, SpringerLink, Wiley Online, Scopus, Science and Google Scholar. Additionally, patent office's such as WIPO, CIPO, and USPTO were consulted to gather all relevant published articles on the disease. The term Alzheimer's disease' is frequently used, either alone or in combination with the terms 'brainanatomy, 'pathophysiology, and 'treatment strategy.' There were no language limitations. The titles, abstracts, and contents of the collected data were used to identify and manipulate them. The bibliographies of selected articles were further screened to uncover additional pertinent research.

3. Pathophysiology

Neuroimaging has greatly contributed to Alzheimer's disease knowledge over the past 20 years, particularly in clinical diagnosis and elucidating its underlying pathophysiological mechanisms [8].

AD exhibits distinct pathological features at both macroscopic and microscopic levels. Macroscopically, there's noticeable atrophy in key brain regions (cerebral cortex, hippocampus, and amygdala), while microscopically, amyloid plaque formation, neurofibrillary tangles due to hyperphosphorylated Tau protein accumulation, and significant neuronal loss are hallmarks of the disease [9].

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Recent studies have revealed that various mechanismssuch as genetic reasons like history of family with apolipoprotein E, influence on AD progression, as well as oxidative stress processes that ultimately lead to neurodegeneration [10].

3.1. Genetic Mechanism

Molecular analysis of DNA from multiple generations of families with Alzheimer's disease onset before 65led to the discovery of specific genes that contribute to the disease, including amyloid precursor protein (APP), presenilin 2 (PSEN2) and presenilin 1 (PSEN1) [11]. A common pathway of augmented accumulation of amyloid beta (Aβ) is triggered by mutations in mentioned genes. However, in late-onset Alzheimer's disease (LOAD), mutations in APP, PSEN1, or PSEN2 are rare. In contrast, LOAD is believed to result from a complex interplay of hereditary and lifestyle factors, with heredity playing a significant role and accounting for up to 80% of the disease's heritability.APOE ε4 is the most firmly established risk determinant for AD[12]. The exact mechanisms linking ApoE to AD are still unclear, but research suggests that ApoE may impair the clearance of amyloid beta from the brain, contributing to its accumulation[10].

3.2. Amyloid beta (Aβ) hypothesis

The amyloid cascade hypothesis is currently the leading theory for understanding Alzheimer's disease progression. According to this hypothesis, the disease is triggered by toxic, soluble Aβ oligomers that cause primary neurological damage [13].APP is a kind of transmembrane protein widely distributed in various tissues, particularly at neuronal synapses. It is proteolytically cleaved by β and γ secretases, yielding Aβ monomers as a product [14]. These Aβ monomers undergo a process of molecular self-association, adopting a β-sheet conformation that confers toxicity, and subsequently polymerize into higher-order fibrillar structures that ultimately coalesce to form senile plaques. Following APP processing, The Aβ monomers exhibit a pronounced tendency towards intramolecular conformational corruption, wherein side chain-mediated interactions precipitate a self-templatedmisfolding event, ultimately yielding hairpin-like architectures stabilized by pivotal contacts between residues localized within the central domain and the N-terminal segment. Hydrogen bond interactions between monomers contribute to the aggregation of amyloid fibrils. Reducing amyloid burden may potentially slow Alzheimer's disease progression [13].

3.3. Protein Tau hypothesis

Microtubules serve as essential cytoskeletal components, orchestrating a range of cellular processes such as morphogenesis, mitosis, and transport of organelle. Microtubule formation and stability are regulated by microtubule-associated proteins (MAPs), with tau protein being a key member of this family [15]. During AD, tau protein undergoes hyperphosphorylation, leading to its redistribution from axons to the somatodendritic compartment of neurons. This change is thought to disrupt microtubule dynamics and promote tau aggregation. Tau protein aggregation plays a pivotal role in the genesis of neurofibrillary tangles (NFTs), a defining neuropathological hallmark of AD. NFTs are a hallmark of AD and are closely linked to disease progression[16].

3.4. Cholinergic hypothesis

Cholinergic neurons primarily release acetylcholine (ACh), which exerts its physiological actions through two distinct receptor subtypes: nicotinic receptors (nAChRs), which are ionotropic, and muscarinic receptors (mAChRs), which are metabotropic[17]. Thus, the cholinergic system, utilizing acetylcholine as a neurotransmitter, plays a crucial role in both the peripheral and central nervous systems. Its widespread distribution and involvement in key processes like attention, learning, memory, and sensory processing make it a significant factor in various forms of dementia, including AD[18]. Cholinergic hypofunction is a third key feature of AD, which is intimately associated with Aβ and tau-related pathology. The brains of individuals with AD are characterized by a marked diminution in choline acetyltransferase activity, reduced acetylcholine synthesis, extensive cholinergic neuron loss, and diminished postsynaptic neuron numbers and availability to ACh. Additionally, cholinergic neuronal and axonal abnormalities occur, along with reduced nicotinic acetylcholine receptor levels[17].

3.5. Oxidative stress

Oxidative stress, a process exacerbated by aging, occurs when the brain's redox balance is disrupted, either through overproduction of reactive oxygen species (ROS) and deficient antioxidant protection [19]. This can lead to significant damage to nervous tissue through multiple interconnected pathways [20]. The disruption of mitochondrial processes poses a considerable risk for the development of AD[21], particularly under conditions where the antioxidant system is insufficiently robust to counteract oxidative stress. The progressive loss of neuronal integrity and viability in AD,is thought to be linked to the ROS production, activation of mitochondrial permeability transition leading to mitochondrial dysfunction, excitotoxicity, impaired ATP production disrupting energy supply, and altered calcium homeostasis affecting cellular signaling[22].

3.6. Inflammatory Mechanism

Alzheimer's disease pathogenesis is closely linked to inflammation, marked by the activation of microglia and astrocytes, which are key players in the disease's progression[23]. Accordingly, various inflammatory triggers can activate microglia and astrocytes, including peripheral sources like systemic infections and chronic inflammation, as well as local sources such as neurotrauma and the buildup of Aβ and tau pathology[24]. The activation of microglia and astrocytes induces the secretion of various neurotoxic cytokines that promote inflammation, notably interleukin-1β, interleukin-6 and tumor necrosis factor-alpha, which can contribute to neuroinflammation[25]. The release of these pro-inflammatory molecules can create a self-perpetuating cycle of neuroinflammation, leading to a cascade of detrimental effects, including amyloid accumulation, neuronal loss, cortical thinning, brain atrophy, infarcts, and ultimately, neurodegeneration [26].

4. Therapeutic approach for Alzheimer's disease

AD remains incurable, yet pharmaceutical interventions can provide symptom relief. Ongoing research aims to identify better therapeutic approaches, preventive strategies, and a potential cure. The disease's etiology is multifactorial, involving various cellular pathways that lead to its progression [9].

4.1. Aβ- targeting therapies

APP, a transmembrane glycoprotein, undergoes proteolytic processing via two distinct pathways, mediated by α-secretase

or β-secretase, producing distinct products with different implications for Alzheimer's disease. The α-secretase pathway generates normal, non-pathological products, whereas the β-secretase pathway produces pathological fragments that contribute to disease development [27]. Therefore, modulating APP processing pathways may provide a valuable therapeutic option for Alzheimer's.Specifically, activating α-secretase through α-secretase agonists or inhibiting β-secretase through β-secretase antagonists could mitigate disease pathology. Furthermore, γ-secretase cleavage of APP fragments generates either p3 peptides (after α-secretase cleavage) or Aβ peptides (after β-secretase cleavage), depending on the initial cleavage pathway, therefore targeting γ-secretase, which acts downstream of β-secretase to generate amyloid-β peptides, offers another potential therapeutic strategy. Therefore, developing inhibitors of β-secretase and γ-secretase, or activators of α-secretase, may lead to effective treatments for Alzheimer's disease[28].

4.2. Tau-targeting therapies

While Aβ has been the primary focus of Alzheimer's disease drug development, tau is now gaining attention as a promising therapeutic target. Researchers are exploring multiple strategies to address tau-related pathology, including regulating tau gene expression, modifying post-translational changes, using immunotherapy, and stabilizing microtubules[29]. Furthermore, several other approaches are being explored to target tau, including blocking tau spreading, anti-aggregate therapies to prevent tau clumping, tau kinase inhibitors to regulate tau phosphorylation, and gene therapy to reduce tau production; these emerging strategies aim to tackle tau's role in disease progression [30].

4.3. Acetylcholinesterase Inhibitors

Acetylcholinesterase (AChE) inhibitors, which block the breakdown of the neurotransmitter acetylcholine (ACh) involved in memory function, are the most commonly used treatment for Alzheimer's disease patients [18]. Acetylcholinesterase inhibitors (AChEIs) were advanced based on the cholinergic hypothesis of cognitive decline. These compounds have been shown to provide symptomatic relief for mild-to-moderate Alzheimer's disease by inhibiting AChE, the enzyme responsible for breaking down the neurotransmitter acetylcholine [31].

4.4. Complementary Treatments Applied to AD

Inflammation-reducing medicationscombat Alzheimer's disease by suppressing inflammatory responses in the brain. By inhibiting astrocyte activation and disrupting pro-inflammatory signaling pathways, these medications mitigate oxidative stress and curb the inflammatory processes that exacerbate disease pathology [10].

A hallmark of early ADis the Aβ plaques deposition, which can promote the production of ROS, driving disease progression.[32]. Elevated ROS levels can lead to oxidative stress, which contributes to disease progression [33]. As a result, ROS-targeting therapies or inhibiting ROS-associated enzymes may offer a therapeutic benefit in AD [34].The bioactive compounds in plant display a range of pharmacological activities and typically that belong to the classes of isoprene derivatives and flavonoids,[3536]. A greatnumber of plant extracts contain chemical compounds exhibiting antioxidant and anti-inflammatory properties[37]These phytogenic plants serve as a natural source of antioxidants, providing protection against oxidative stress, and researchindicates that they are far more effective than artificial antioxidants[38.]Which has contributed to the reduction of symptoms of Alzheimer's or inhibits the development of the disease

Conclusion

Alzheimer's disease is a complex neurodegenerative disorder with limited therapeutic options, as the disease develops very quickly, leading to many symptoms and complications that may lead to death. There are many attempts to find a solution to this disease, which are based primarily on the causes of the disease, such as amyloid beta, protein Tau, and inhibiting the acetylcholine esterase enzyme, without forgetting inflammation. However, research has not ended and is ongoing to reduce the severity of this disease.

Conflicts of Interest

None

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