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Alzheimer's Disease and Oxidative Stress

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by synaptic loss, memory decline, and brain atrophy. Oxidative stress plays a pivotal role in the pathogenesis of AD by driving mitochondrial dysfunction, lipid peroxidation, and tau protein hyperphosphorylation. This review discusses the three main pathways through which oxidative stress contributes to AD progression: mitochondrial damage, macromolecule peroxidation, and neuroinflammation. Understanding these mechanisms is essential for identifying therapeutic strategies aimed at disrupting this vicious cycle and mitigating AD development.

Keywords

Alzheimer's Disease, Oxidative Stress, Mitochondrial Dysfunction, Amyloid Beta, Tau Protein

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease affecting older individuals. Especially women, due to low levels of estrogen in menopausal. Furthermore, statistics show that the number of patients with AD will increase in the future, expected to duplicate every five years Furthermore, Alzheimer's disease nearly affecting 36.6 million individuals, which mostly above 60 years of age. However, AD started with slight memory loss, changes in the cortex and hippocampus, and Aβ accumulation [1], but no functional disabilities. This is called the cellular or presymptomatic phase and may continue for years. Therefore, Aβ accumulation contributes to tau hyperphosphorylation, leading to necroptosis in neurons and degeneration, and the symptoms begin to appear, which is called mild cognitive impairment (MCI). When the disease develops in the cerebral cortex, swallowing and urination difficulties and even death occur, and this phase is called dementia. In addition, there are many factors contributing to AD such as gender, bad diet,

educational level, pesticide to exposure, depression, weight, alcohol intake, diabetes, and cigarette [2]. Although, the main cause and mechanism of AD is not clear, The oxidative stress is mainly involved in the development of Alzheimer's disease by damaging the brain. The brain is extremely sensitive to oxidative stress [3] [4] because the central nervous system utilizes 20% oxygen in the body. While, it has a low antioxidant ability. Thereby, oxidative stress is one of the primary mechanisms that leads to Alzheimer's disease (AD). And represent the primary linking between various pathways. In this review, we highlight the impact of oxidative stress on Alzheimer's, including mitochondrial dysfunction, metabolic damage, and neuroinflammation [5] [6].

2. Literature Review

2.1. Alzheimer's Disease

Alzheimer's disease (AD) is a long-term neurodegenerative disease that causes gradual brain degeneration. Neuronal death and brain atrophy have also been observed. It is the primary cause of dementia. Responsible for approximately 60% - 80% of dementia cases. Additionally, it is considered the most common neurodegenerative disease, leading to disability and morbidity worldwide [5] [6].

Individuals with early AD experience changes in mood, apathy, communication difficulties, unawareness of their surroundings, slight loss of memory, and disability in muscle control. In the advanced stage of AD, an individual develops dementia, a syndrome characterized by cognitive deterioration that affects daily life independently. In addition, Alzheimer's mainly affects the neocortex and hippocampus. However, it is also characterized by extracellular Aβ plaques and intracellular tau tangles [1] [7].

2.2. Oxidative Stress

Oxidative stress is a phenomenon characterized by excess production of reactive oxygen species (ROS), reactive nitrogen species (RNS), and a lack of neutralization (as illustrated in **Figure 1**). This causes an imbalance between the antioxidants and oxidants. Furthermore, it affects cellular structures such as cell membranes, lipids, proteins, lipoproteins, and DNA. Therefore, it may contribute to the development of AD. Neurons are highly sensitive to oxidative damage because they cannot replace the damaged neurons. This leads to neurotoxicity, mitochondrial dysfunction, and impairment of the central nervous system. ROS are byproducts of cellular respiration [8] and are produced during mitochondrial oxidative phosphorylation. However, some electrons exit and create free radicals, specifically at Complex I and Complex III. Consequently, this leads to ROS overproduction and oxidative damage [1] [4] [9].

In AD, oxidative stress contributes to synaptic damage in the neocortex and limbic system. Furthermore, this leads to dendritic spine loss, presynaptic terminal loss, and axonal dystrophy. In addition, it causes tau hyperphosphorylation and leads to the formation of NFTs [4] [7].

Oxidative stress contributes to AD through three mechanisms that affect cell homeostasis: ROS production, Aβ, and tau protein. The mechanisms are:

1) Macromolecule peroxidation and production of neurotoxic aldehydes, such as 4-hydroxynonenal (HNE), cause synaptic function loss.

2) Aβ-metal ion redox potentials, such as those of Cu^{2+} and Zn^{2+}, bind to Aβ and produce reactive oxygen species (ROS), leading to increased oxidative stress [4] [9].

3) mitochondrial dysfunction, accumulated Aβ causes mitochondrial dysfunction [7] [8].

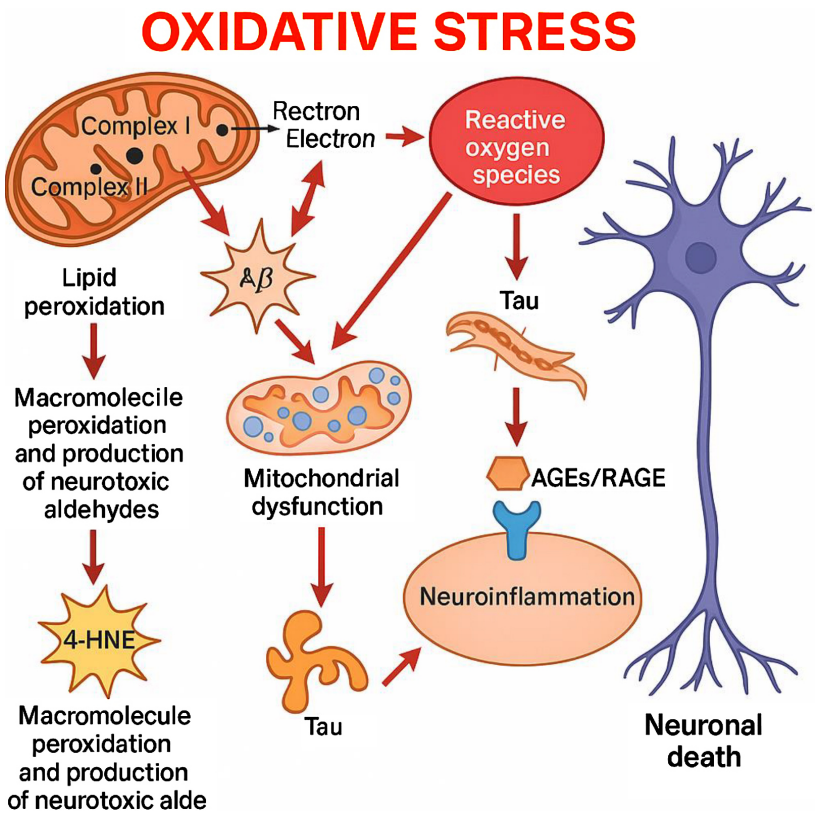

Figure 1. Mechanistic diagram of oxidative stress in Alzheimer's disease.

This figure shows how mitochondrial electron leakage from Complex I and III generates reactive oxygen species (ROS), which initiate a cascade involving amyloid-beta (Aβ) accumulation, tau protein hyperphosphorylation, lipid and protein peroxidation, and activation of the receptor for advanced glycation end products (RAGE). These interconnected processes lead to chronic neuroinflammation, synaptic dysfunction, neuronal death, and progressive cognitive decline.

2.3. Mitochondrial Dysfunction

Oxidative stress contributes to mitochondrial damage. Moreover, mitochondrial dysfunction affects APP expression and processing, leading to accumulation of Aβ and tau hyperphosphorylation. Furthermore, it also increases oxidative stress

and contributes to mitochondrial dysfunction. Starting a vicious cycle. However, in the early stages of AD, mitochondrial dysfunction contributes to loss of ATP production and cellular damage. In addition, it impairs neurotransmission and plasticity, leading to cognitive impairment and cell death. Moreover, impaired autophagy, a cellular process that removes damaged proteins, leads to the failure to remove damaged mitochondria [10] [11]. These factors contribute to AD development. Therefore, there is an impact on Aβ and tau metabolism, and hence, accumulation [7] [8].

Additionally, mitochondrial dysfunction decreases the activity of ETC complexes, particularly cytochrome c oxidase (COX) (complex IV) and superoxide dismutase 1 (SOD1). This leads to impaired ATP production and increased oxidative stress. However, under oxidative stress, damaged mitochondria release cytochrome c into the cytosol and activate caspase. This leads to tau hyperphosphorylation and the accumulation of NFTs as insoluble filaments in the neuralperikaryal cytoplasm, axons, and dendrites. Therefore, impairment of cytoskeletal microtubules and tubulin-associated proteins leads to neurodegeneration. However, a vicious cycle of oxidative stress and tau accumulation contributes to the development of AD [7] [8].

Aβ is a peptide that is cleaved from the transmembrane amyloid precursor protein APP by β- and γ-secretase cleavage enzymes, which are responsible for Aβ biosynthesis. However, Aβ accumulation occurs because of mitochondrial dysfunction caused by impaired ETC and reduced ATP production. Therefore, it affects β-secretase and γ-secretase cleavage enzyme activities and reduces Aβ degradation. As a result, Aβ accumulates in the hippocampus, amygdala, and the cerebral cortex. Therefore, the stimulation of astrocytes and microglia leads to cellular dysfunction and neurotoxicity. Ultimately, it causes neurodegeneration and AD development. Additionally, Aβ accumulation impairs MAMs by interacting with mitochondrial proteins, such as TOMM40 and cytochrome c oxidase. In addition, ROS produced by mitochondrial dysfunction oxidizes APP, leading to Aβ accumulation, thereby increasing mitochondrial dysfunction. Starting a vicious cycle of damage [7] [8].

2.4. Macromolecules Peroxidation

Oxidative stress causes oxidative damage to lipids in the brain [12]. Furthermore, it contributes to neurodegeneration in AD. In addition, lipid peroxidation products such as 4-hydroxy-2-nonenal (HNE) and malondialdehyde [13] [14] interact with proteins and nucleic acids to produce covalent adducts. Therefore, it leads to neurotoxicity, neuronal structure and function damage, and disruption of homeostasis. In contrast, reactive oxygen species (ROS) promote protein peroxidation and alter proteins. Additionally, lipid peroxidation products such as HNE cause protein dysfunction. Furthermore, neuronal damage, cognitive decline, and the accumulation of Aβ increase oxidative damage in the brain.

The overproduction of intracellular ROS contributes to DNA damage, strand

breaks, and lesions. Furthermore, lipid peroxidation products are responsible for DNA and protein lesions. Moreover, mitochondrial DNA (mtDNA) is damaged by oxidative stress as it is not protected by histones. Therefore, it impairs the function of post-mitotic neurons. However, the release of cytochrome c or mtDNA into the cytosol leads to the accumulation of mtDNA mutations and increased ATP needs [15]. Therefore, it contributes to increased apoptosis and impairs ETC protein synthesis. Furthermore, DNA damage activates kinases and PARP and lowers NAD+ levels, leading to increased oxygen consumption and ATP production. Thus, mitochondria are coupled to meet high energy demands, which increases membrane potential and free radicals. Furthermore, it decreased mitophagy and caused DNA damage. Additionally, oxidative stress contributes to single-strand breaks (SSB) and double-strand breaks (DSB) in DNA [16] [17]. DSBs accumulate in the hippocampus, leading to damage to neural cells and memory loss [18]. Furthermore, impacting genome integrity leads to changes in structure, transcription, and synaptic genes. Therefore, it contributes to the activation of neurodegeneration, immune responses, and neuroinflammation. Additionally, impaired repair processes lead to increased DNA damage, which initiates a vicious cycle. As seen with 8-oxoG, one of the oxidized base lesions in AD. Thus, increased 8-oxoG levels led to reduced OGG1 enzyme activity and 8-oxoG accumulation. Therefore, it may contribute to microglial activation and neuronal loss [19] [20].

2.5. Neuroinflammation

Oxidative stress contributes to neuroinflammation through excessive production of reactive oxygen species (ROS), advanced glycation end products (AGEs), and mitochondrial damage. However, neuroinflammation is a CNS response to the loss of homeostasis, as microglia respond to and discharge inflammatory factors. Overproduction of advanced glycation end products (AGEs), which are a complex mixture of cross-linked proteins and protein modifications, interaction with advanced glycation end products receptors (RAGE) [21] [22], in microglia and astrocytes as a transporter and a receptor for Aβ, impairing the removal of Aβ, leading to Aβ accumulation and inflammation by releasing pro-inflammatory cytokines, leading to more oxidative stress in a vicious cycle. Moreover, increased toxicity is due to the ability of AGEs to change the structure and function of cell surface receptor proteins and promote apoptosis. Activated microglia contribute to neurodegeneration by synapse loss, tau hyperphosphorylation, and an impaired blood-brain barrier (BBB), allowing toxic substances to enter the brain parenchyma, transcription of pro-inflammatory genes, and cytokine release [1] [2] [4].

2.6. Therapeutic Potential

The potential of therapeutic AD can be summarized in three ways. Including preventing the disease, reducing the development, and treating the symptoms [2].

2.6.1. Preventing the Disease

Genetic engineering, Aβ production inhibiting, or Aβ accumulation inhibiting [2] [6], consider potential ways of preventing. Furthermore, cholinesterase such as donepezil, galantamine, rivastigmine, and tacrine are used to prevent the break of neurotransmitters, and N-methyl-D-aspartate receptor antagonist memantine is used for enhanced cognition. However, some lifestyle changes have benefits on prevention such as exercise, balanced diet, stop smoking and alcohol intake, controlled of hypertension and diabetes, social and cognitive activities.

2.6.2. Reducing the Development

Antiinflammatory, and antioxidants play roles in reducing development. However, aducanumab, BAN2401, and gantenerumab can reduce Aβ accumulation, and tau hyperphosphorylation. Additionally, oligomannate, can reduce neuroinflammation by effective gut microbiome, reduce dysbiosis and peripheral inflammatory cell, return normal gut bacterial composition [1] [2] [4].

2.6.3. Treating the Symptoms

Cholinesterase inhibitors delay the deterioration of cognition [2], and atypical antipsychotics change serotonergic system for the treatment of some non-cognitive symptoms. Furthermore, pimavanserin is used for psychosis, brexpiprazole, citalopram, and nabilone can reduce agitation. In addition, suvorexant enhances the quality of sleep by increasing sleep time and reduce wake up after sleep for treatment of insomnia.

3. Conclusions

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide, leading to disability and morbidity. Current research clearly shows that oxidative stress is involved in AD development. It contributes to oxidative damage, such as lipid and protein peroxidation, and DNA damage, as oxidative stress contributes to lipid peroxidation and produces HNE and malondialdehyde, which interact with proteins and DNA to cause lesions. In addition, damaged mitochondria overproduce free radicals, leading to increased Aβ accumulation and tau hyperphosphorylation, which causes more oxidative stress and initiates a vicious cycle. Furthermore, it causes cognitive impairments and neuronal death. Moreover, oxidative stress contributes to neuroinflammation by the overproduction of reactive oxygen species (ROS), advanced glycation end products (AGEs), and mitochondrial damage. Additionally, AGE-RAGE reactions in microglia and astrocytes accumulate Aβ and release pro-inflammatory cytokines, which leads to inflammatory responses and impaired BBB and pro-inflammatory gene transcription. These processes lead to neuronal degeneration and the development of Alzheimer's disease.

Understanding oxidative mechanisms is essential for identifying intervention targets.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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