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The Role of Endoplasmic Reticulum Stress in Alzheimer's Disease: Molecular Mechanisms and Viral Hypotheses

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Abstract. Alzheimer's disease (AD), a brain disorder marked by memory loss and cognitive decline, is pathologically characterized by amyloid-beta (Aβ) plaques and tau neurofibrillary tangles. Recent studies link AD to endoplasmic reticulum (ER) stress from misfolded proteins buildup. This review explores molecular mechanisms of ER stress in AD, focusing on how persistent ER stress exacerbates Aβ and tau pathologies and contributes to neuroinflammation, mitochondrial dysfunction, and autophagy disorder. Additionally, the review examines the viral hypothesis of AD, highlighting how certain viral infections, particularly Zika virus, may accelerate AD progression through the ER stress pathway. These insights enhance understanding of AD pathogenesis and potential therapeutic strategies targeting ER stress and viral factors.

Keywords: Alzheimer's disease, ER stress, amyloid-beta, viral hypothesis, unfolded protein response

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that begins with mild memory loss and progresses to language difficulties, disorientation, impaired judgment, and emotional changes[1,2]. The disease, initially reported by German physician Alois Alzheimer in 1906 and named after him, is now commonly known as Alzheimer's disease [12/24/2024 4:54:00 PM3]. AD is the most typical form of dementia, accounting for 60-80% of cases in the elderly group [4]. As the disease progresses, patients may ultimately lose the ability to live independently, requiring around-the-clock care [1,5]. Alzheimer's disease is currently incurable, and existing treatments centre on symptom relief and progression delay [2,6,7]. The disease's specific onset mechanisms are unclear, but genetics, environmental factors and lifestyle all significantly contribute.

In AD, β-amyloid peptide (Aβ) is generated from amyloid precursor protein (APP) by β and γ secretases. APP is normally processed through the α secretase pathway, not producing Aβ. However, in AD patients, APP is more processed through the β secretase pathway, producing Aβ fragments that accumulate in the brain as amyloid plaques [1,6,7]. The plaques accumulate between neurons, interfering with signal transmission and leading to neuronal death and brain atrophy [1]. Tau protein, a microtubule-associated protein, normally helps maintain cell stability [8]. In AD patients, tau abnormally phosphorylates, detaching from microtubules and forming neurofibrillary tangles [9,10]. These tangles accumulate within neurons, interfering with cellular transport and ultimately leading to neuronal death [11].

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Recent studies find a connection between Alzheimer's disease and endoplasmic reticulum (ER) stress due to the accumulation of misfolded or unfolded proteins [12-14]. The unfolded protein response (UPR) is activated to restore normal ER function [15], but if the stress is too strong, cell apoptosis may result. However, when the stress is too intense or prolonged, the UPR cannot restore endoplasmic reticulum homeostasis, leading the cell to initiate apoptosis [16,17]. The build-up of Aβ and abnormal tau protein phosphorylation can trigger ER stress, while continued ER stress worsens their misfolding and accumulation [13,18]. This review focuses on the molecular mechanisms of Alzheimer's disease and the endoplasmic reticulum stress response, exploring the pathways linking them. It aims to provide insight into the underlying molecular mechanisms of Alzheimer's and potential treatments.

2. Pathological Features of AD

2.1. Amyloid Beta Deposition

Amyloid Beta (Aβ) is a key feature of Alzheimer's disease (AD), characterized by Aβ plaque buildup in the brain [1,19]. Aβ and tau proteins can accumulate in amyloid plaques and neurofibrillary tangles, linked to neurodegenerative processes in AD patients' brains [6,20]12/24/2024 4:54:00 PM. Studies have found that mutations in the PSEN1, PSEN2, or APP genes in familial Alzheimer's patients can lead to abnormal processing and aggregation of Aβ proteins [21]. The APP gene precursors Aβ peptides, with mutations affecting cleavage and aggregation. The PSEN1 and PSEN2 genes provide catalytic subunits for the γ-secretase enzyme, breaking down APP to generate Aβ peptides (Figure1) [19,22].

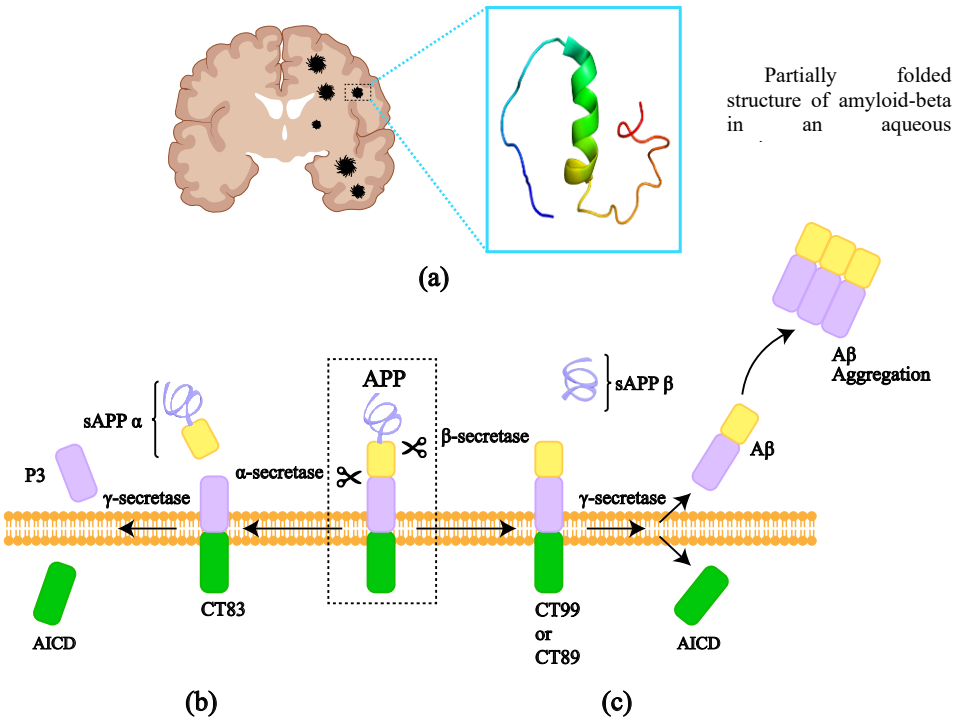

Figure 1. (a) In Alzheimer's patients, altered APP processing results in increased Aβ aggregate accumulation in the brain [23]. (b) In the normal cleavage mechanism of APP on the membrane, the non-amyloidogenic pathway involves APP being first cleaved by α-secretase, producing sAPPα and C83 fragments. These C83 fragments are then cleaved by γ-secretase, yielding non-toxic P3 and AICD. (c) In the abnormal APP processing on the membrane, the amyloidogenic pathway involves APP being first cleaved by β-secretase, producing sAPPβ and C99 fragments. The C99 fragments are then cleaved by γ-secretase, generating toxic Aβ peptides. These peptides aggregate to form fibers in the brain, leading to amyloid plaques, neuronal dsfunction, and cell death.

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Aβ is believed to trigger familial Alzheimer's disease and drive its progression [19]. Though initially considered a downstream event of Aβ deposition and tau protein pathologies, tau and Aβ are now thought to act in parallel pathways, potentiating each other's toxic effects and causing Alzheimer's disease [1,20]. Like prion proteins, toxic abnormal conformations of Aβ are generated during the disease and can induce pathological conformations of normal peptides, propagating the disease in the brain [24]. Aβ may also exist in forms such as oligomers or fibrils, with varying toxic effects requiring further study [25,26]. Low-molecular-weight Aβ oligomers seem to interact with various membrane receptors, including prions [26]. However, the significance of these interactions to disease progression remains unclear. Given Aβ's role in Alzheimer's disease, blocking its production via Aβ-degrading enzymes has become a reasonable treatment approach [27,28]. Current research focuses on developing BACE1 and γ-secretase inhibitors, though both have encountered adverse effects in clinical trials [29]. Future studies may improve Aβ reduction effectiveness by modulating γ-secretase to generate shorter, less toxic Aβ versions and combining BACE1 inhibitors [2,28].

2.2. Tau Phosphorylation and Tangle

Tau protein is essential for maintaining microtubule structure and function [10,30]. In Alzheimer's disease (AD), abnormal phosphorylation of Tau causes its dysfunction and the formation of neurofibrillary tangles [31], primarily composed of abnormal Tau proteins [28]. Increased likelihood of Tau protein dissociation from microtubules due to abnormal phosphorylation destabilizes the microtubules and causes them to collapse [31]. Dissociated Tau proteins form neurofibrillary tangles in brain regions associated with memory and cognition, like the hippocampus and cortex [32,33]. While amyloid plaques and neurofibrillary tangles are major features of Alzheimer's disease (AD), their specific mechanisms and relationship are still being studied [28,32]. Tau alterations can independently lead to neurodegenerative changes without Aβ accumulation [34,35]. Initially, Tau alterations were thought to be downstream of Aβ accumulation [36], but now views suggest they may act in parallel pathological pathways leading to AD onset, strengthening their toxic effects [20,37]. Like prions, Tau's toxic conformation arises during AD, inducing pathological conformational changes in normal proteins, allowing disease spread in the brain [1,38,39]. Research and therapeutic strategies targeting Tau are crucial. Potential areas include preventing abnormal Tau phosphorylation, preventing Tau aggregation into tangles, and eliminating already formed Tau tangles using immunotherapy or other methods to mitigate neuronal damage [2,28].

3. Mechanisms of ER Stress in AD

3.1. ER stress response

Endoplasmic reticulum (ER) stress arises from the buildup of unfolded or misfolded proteins in the ER [40,41]. The ER is vital for protein synthesis, folding, modification and transport [42]. ER stress triggers the unfolded protein response (UPR) to restore normal function [43]. If stress persists, the UPR may fail and the cell may initiate apoptosis to protect the organism [14,17].

Recent studies indicate that ER stress is a key factor in several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [14,44]. It's believed to be triggered by pathological proteins like Aβ and tau proteins and further exacerbates their mis-folding and accumulation, forming a vicious cycle [15,45].

3.2. ER stress response and Alzheimer's disease

Amyloid-β aggregation is common in Alzheimer's disease (AD) patients [38], and protein misfolding is the primary cause of endoplasmic reticulum (ER) stress [13]. The relationship between AD and ER stress is complex. ER stress is a cellular stress response caused by misfolded proteins and triggers the unfolded protein response (UPR) to restore homeostasis [41,46]. If ER stress persists, the adaptive mechanism fails, leading to neurological damage [15].

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In AD, Aβ production, aggregation, and oligomerization are important factors in disease development. Studies show Aβ oligomers have high neurotoxicity and can induce ER stress [1,19]. ER stress can induce neuroinflammation through UPR activation. This involves release of various factors and chemokines, triggering microglia and astrocyte activation, exacerbating neurodegeneration [14-16].

In Alzheimer's disease (AD), all three major UPR signaling pathways (ATF6, IRE1, and PERK) are activated. Phosphorylated PERK, eIF2α, and IRE1α have been found in AD brains, indicating UPR's significant role in AD pathology [47,48]. Continuous UPR activation triggers cell apoptosis, exacerbating neuronal death and dysfunction [14]. ER stress is also linked to abnormal tau protein phosphorylation and neurofibrillary tangles formation in AD [20]. It promotes tau phosphorylation via the JNK pathway, leading to neuronal dysfunction and death (Figure 2) [48].

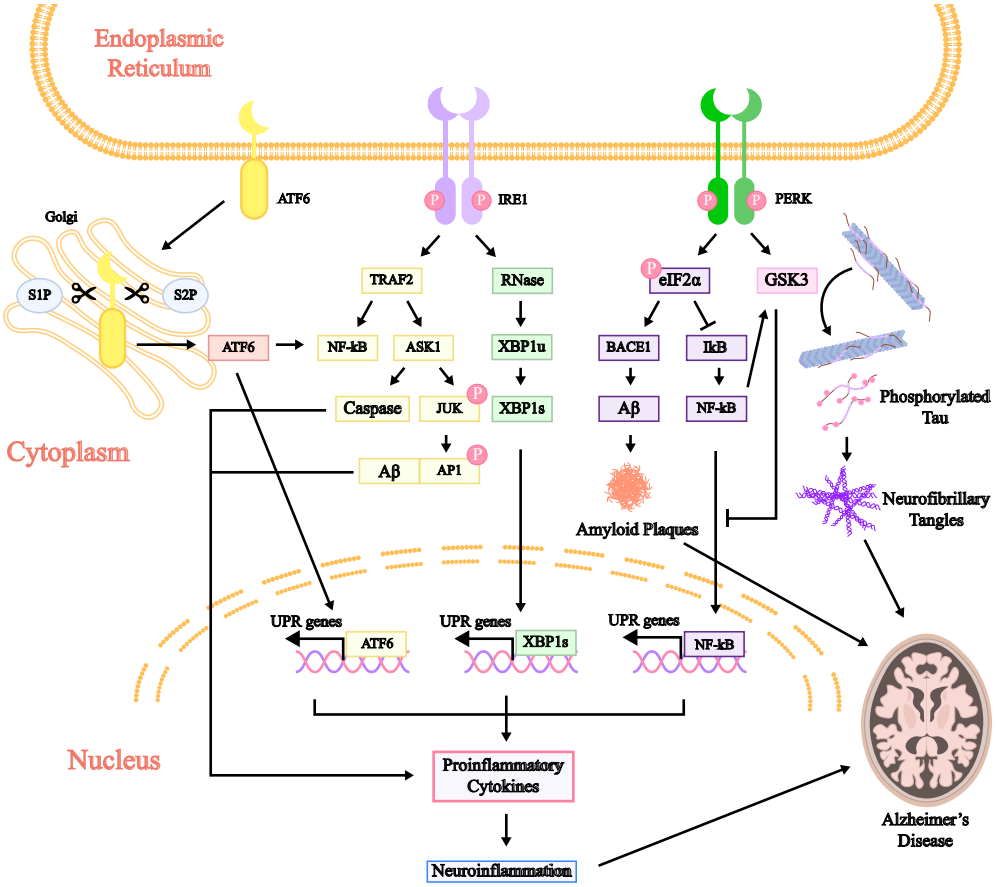

Figure 2. The ER and UPR signalling cascade in neuroinflammation and Alzheimer's disease (AD). The figure illustrates activation pathways of PERK, IRE1, and ATF6, key unfolded protein response (UPR) mediators. PERK activation phosphorylates eIF2α, triggering GSK-3 to form neurofibrillary tangles and phosphorylating BACE1 to generate amyloid-beta (Aβ). eIF2α phosphorylation also activates NF-κB, a pivotal inflammatory transcription factor. IRE1 activation splices XBP1s, induces caspase cascades, and further activates NF-κB, promoting inflammation. ATF6 activation releases its cytosolic domain, translocating to the nucleus and inducing expression of genes driving neuroinflammation and contributing to AD pathology. The diagram highlights these pathways' intersection in driving cellular events underlying AD, including amyloid plaques, neurofibrillary tangles, and chronic inflammation.

3.3. ER stress response and neuroinflammation

The interplay between ER stress and neuroinflammation is highly significant. ER stress triggers adaptive changes, including induction of inflammatory responses [47,50]. The three major signal pathways of the

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UPR - PERK, IRE1, and ATF6 - play crucial roles in this process. PERK activation leads to eIF2α phosphorylation, subsequently activating NF-κB, a key inflammatory factor. IRE1 activation promotes expression of inflammatory factors through XBP1s translocation and caspase cascade reactions. ATF6 activation releases its cytoplasmic domain, triggering NF-κB and regulating expression of multiple genes implicated in neuroinflammation. These inflammatory responses have a dual role in onset and progression of Alzheimer's disease (AD), potentially protecting neurons and exacerbating neurodegenerative changes [2,51].

3.4. ER stress response and mitochondrial dysfunction

ER stress is closely tied to mitochondrial dysfunction. It can disrupt normal calcium transport from the ER to the mitochondria, causing overloading and malfunction [52]. For example, ER stress can indu12/24/2024 4:54:00 PMce an increase in calcium influx, leading to mitochondrial depolarization and the activation of caspase-12, ultimately triggering cell apoptosis [17,52]. Moreover, ER stress can further impair mitochondrial function by inducing oxidative stress, particularly evident in brains of AD patients [53,54].

3.5. ER stress response and autophagy disorder

The ubiquitin-proteasome pathway is influenced by the ER stress response, affecting AD progression [55]. Autophagy is important for cells to eliminate damaged or misfolded proteins. However, autophagy is often inhibited in AD [57]. Endoplasmic reticulum stress affects autophagy through various pathways, including activation of the UPR and changes in ER-mitochondria contact sites [55]. The IRE1 and PERK pathways in the UPR regulate autophagy gene expression and autophagosome formation. Autophagy dysfunction results in the buildup of misfolded proteins like Aβ and tau, worsening neurodegenerative damage [20,55,57].

The ER stress plays a critical role in the pathogenesis of AD [48], directly causing protein misfolding and neuronal damage, and exacerbating the disease progression through neuroinflammation, mitochondrial dysfunction, and autophagy dysfunction. Understanding the molecular mechanisms of endoplasmic reticulum stress response can elucidate the pathological process of AD, providing important insights for developing novel therapeutic strategies.

3.6. Viral hypothesis of AD and ER stress response

Recent evidence suggests viral infections play a significant role in AD pathogenesis. They trigger neuroinflammation and accelerate AD-related pathological changes through the endoplasmic reticulum stress pathway [5,58]. Some neurotropic viruses, like Zika virus (ZIKV), Japanese encephalitis virus (JEV), herpes simplex virus (HSV), human immunodeficiency virus (HIV), and cytomegalovirus (CMV), can infect and damage neurons in the central nervous system, potentially leading to AD [58-62].

ZIKV infection has gained considerable attention, capable of inducing AD-like pathological features, including Aβ and phosphorylated p-Tau expression, within brain organoid models. ZIKV proteins primarily reside within the endoplasmic reticulum (ER), and replication occurs within the host ER, leading to ER stress and UPR activation. Persistent ER stress from ZIKV infection activates the PERK-eIF2α pathway, ultimately leading to Aβ generation and Tau phosphorylation, key AD pathological features [61,63].

Specifically, sustained activation of the PERK pathway following ZIKV infection leads to phosphorylation of eIF2α, reducing overall protein synthesis while promoting generation of Aβ by increasing abundance of BACE1. Furthermore, GSK3α/β are key in Tau phosphorylation and significantly increase in ZIKV-infected brain organoids, exacerbating Tau pathological changes [64,65]. Use of PERK inhibitors can significantly reduce pathological changes caused by Aβ and p-Tau induced by ZIKV infection, suggesting the PERK-eIF2α pathway is important in ZIKV-induced AD pathology [58,61,63-66].

The Zika virus and some other viral infections accelerate the development of Alzheimer's disease (AD) by inducing endoplasmic reticulum (ER) stress and the unfolded protein response. The discovery of this link not only identifies novel factors in AD pathogenesis but also offers insights into developing new treatment strategies that target the ER stress pathway.

4. Conclusion

Alzheimer's disease is a complex, fatal neurodegenerative disorder marked by Aβ plaque formation and abnormal tau protein phosphorylation, leading to neurofibrillary tangles [1]. These pathological features directly impair neuronal function and survival, and worsen disease progression by inducing endoplasmic reticulum stress and unfolded protein response [6,44,48]. The ER stress not only directly causes protein misfolding and neuronal damage, but also triggers neuroinflammation, mitochondrial dysfunction, and autophagy dysfunction, forming a vicious cycle that further aggravates disease progression [47].

Additionally, viral infections like Zika accelerate the pathological progression of AD by inducing ER stress and UPR [61,63], providing new perspectives on AD's complex pathogenesis. In-depth research on the molecular mechanisms and specific role of endoplasmic reticulum stress response in AD will elucidate its pathology and provide important theoretical foundations and developing new treatment strategies [6].

Future research should investigate ER stress interactions with pathophysiological mechanisms and regulate the UPR pathway to reduce neurotoxicity [7]. Particularly, understanding how viral infections trigger ER stress and pathological changes in AD could provide breakthroughs in AD prevention and treatment [58]. Multi-angle, multi-level research can unravel specific ER stress mechanisms in AD, aiding comprehensive understanding of AD pathogenesis for new treatment insights.

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