Cao & Zhang. *Zool. Res.* 2024, 45(4): 875−876
https://doi.org/10.24272/j.issn.2095-8137.2024.183

ZR | Zoological Research

News Open Access

Targeting synaptic pathology in Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory and cognitive impairments. The two primary pathological hallmarks of AD include the accumulation of β-amyloid (Aβ) plaques and formation of neurofibrillary tangles (NFTs) composed predominantly of hyperphosphorylated tau protein (Zhang et al., 2023). Moreover, synaptic dysfunction is considered another crucial factor in AD pathogenesis and is closely associated with cognitive decline. Notably, synaptic damage, loss, and dysfunction manifest earlier than the pathological features of Aβ plaques and NFTs (Knopman et al., 2021). Therefore, understanding the mechanisms underlying synaptic dysfunction in AD is vital for providing insights into disease mechanisms and developing novel therapeutic strategies.

Synapses are the fundamental structures for memory storage and information transmission within the central nervous system (CNS). The number and structure of synapses undergo dynamic changes to optimize neuronal connections associated with cognitive functions. This process, known as synaptic plasticity, plays a crucial role in shaping the neural circuits that underlie learning and memory (Yu et al., 2024). Pathogenic Aβ and tau proteins induce synaptic defects in AD by interacting with specific synaptic proteins and mitochondria. These interactions result in alterations in the composition of synaptic proteins, oxidative stress, chronic inflammatory responses, and excessive activation of glial cells (Tzioras et al., 2022). Consequently, synapses are excessively eliminated, leading to axonal degeneration and, ultimately, neuronal loss.

Aβ is generated through the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases. At low concentrations, Aβ facilitates neuronal survival and axonal branching, regulates potassium ion channel function, and maintains normal neuronal activity. Aβ can exist as monomers, soluble oligomers, and fibrillar deposits. Compared to monomers and protofibrils, Aβ oligomers are strongly associated with synaptic loss and progressive cognitive decline in patients with AD. In the early stages of AD, Aβ oligomers aggregate around neurons and bind tightly to multiple receptors at excitatory synapses (Tu et al., 2014). The Aβ-receptor complexes can lead to enhanced synaptic toxicity as well as structural, compositional, and functional changes in synapses.

Tau is a principal microtubule-associated protein that binds to and stabilizes microtubules in neurons. Hyperphosphorylated, misfolded, and oligomeric tau proteins accumulate at both presynaptic and postsynaptic terminals, eventually forming NFTs. Tau accumulation at presynaptic sites reduces cytoskeleton stability, enlarges synaptic terminals, depletes the synaptic vesicle pool, impairs synaptic transmission, and disrupts synaptic plasticity. Hyperphosphorylated tau induces an increase in the release of cytosolic calcium (Ca^{2+}) from the endoplasmic reticulum, leading to transient elevations in spontaneous neurotransmitter release and defects in exocytosis (Moreno et al., 2016). Similar to Aβ oligomers, tau oligomers exhibit synaptotoxicity. Extracellular tau oligomers are internalized by neurons and mislocalized within postsynaptic dendritic compartments during disease progression. They interact with complexes formed by postsynaptic protein FYN, PSD95, and N-methyl-D-aspartate (NMDA) receptors, thereby interfering with glutamate receptor signaling and trafficking (Shen et al., 2023). Ultimately, this results in decreased expression of these receptors on the cell surface, leading to subsequent changes in dendritic spine morphology and synaptic loss.

Aβ and tau may synergistically disrupt critical molecular signaling pathways for presynaptic and postsynaptic plasticity in the AD brain, exacerbating disease progression. Both Aβ and tau inhibit the activity of the transcription factor cAMP response element-binding protein (CREB) and its upstream regulator Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which are essential for synaptic plasticity and memory formation. Mitochondria-generated cellular energy is vital for maintaining various synaptic functions, such as mobilizing synaptic vesicles from reserve pools to release sites, supporting vesicle release/recycling, facilitating synaptic assembly/plasticity, and regulating intracellular Ca^{2+} concentration. Dysregulation of proteins mediating mitochondrial energy metabolism, such as muscle glycogen phosphorylase, compromises energy production and has been observed in AD (Wang et al., 2023). Both Aβ and tau can trigger mitochondrial alterations, resulting in reduced adenosine triphosphate (ATP) production, disrupted mitophagy, and increased oxidative stress/reactive oxygen species (ROS) generation, ultimately leading to progressive synaptic loss, axonal changes, and neuronal degeneration.

Synaptic degeneration and AD pathology propagation are also influenced by glial cells in the brain. Variations in the triggering receptor expressed on myeloid cells 2, predominantly expressed in microglia, and astrocyte-derived apolipoprotein E4 are closely associated with the risk and severity of AD. Abnormally activated microglia and astrocytes are common pathological features in AD. Microglia are primary immune cells in the CNS, and activated microglia can release pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 1 (IL-1), which can damage synapses. Moreover, activated microglia excessively phagocytose and prune synapses through a complement-dependent

Received: 28 May 2024; Accepted: 05 July 2024; Online: 10 July 2024

mechanism, leading to synaptic loss in AD animal models (Tzioras et al., 2022). Astrocytes are crucial for maintaining the blood-brain barrier, supporting neurons, recycling neurotransmitters, and regulating synaptic function. Reactive astrocytes in AD models impair synaptic function by reducing phagocytic ability and disrupting glutamate transport and signaling, thereby contributing to synaptic loss (Brandebura et al., 2023).

The clearance of toxic proteins is essential for maintaining synaptic homeostasis. Autophagy plays a pivotal role in modulating Aβ metabolism and tau pathology by influencing their production, secretion, and clearance (Zhao et al., 2024). Local autophagic activity at synapses is also crucial for regulating memory formation (Zhang et al., 2023). Dysregulation of autophagy has been observed in AD, and interventions that stimulate autophagy can reverse impairments in synaptic plasticity and enhance cognitive function in AD models.

Changes in synaptic function can impact the integrity of downstream neural circuits. In animal models, disruption of the entorhinal-hippocampal circuitry results in a compensatory increase in synaptogenesis in the hippocampus, similar to changes observed in AD patients (Kim et al., 2022). Adult hippocampal neurogenesis (AHN), representing a significant form of neuroplasticity, is substantially decreased during the early stages of AD, potentially contributing to memory and cognitive impairments. Enriched environments can enhance AHN in AD mice, concurrently reducing Aβ accumulation and tau phosphorylation within the hippocampus. Furthermore, genetic and pharmacological stimulation of AHN, combined with brain-derived neurotrophic factor administration, can potentially improve cognitive function in AD mice (Kim et al., 2022; Li et al., 2023). Therefore, targeting AHN in adult AD patients and AD animal models may provide a novel strategy for treating AD.

As Aβ and tau are the primary pathogenic factors in AD, most therapeutic developments have focused on reducing their aggregation and accumulation. At present, the US Food and Drug Administration (FDA) has approved several Aβ monoclonal antibodies, including aducanumab and lecanemab, for AD treatment, while therapies targeting tau are still under investigation (Zhang et al., 2023). Given the importance of synaptic dysfunction in AD pathogenesis, exploring new treatments targeting synapses represents another promising avenue. Indeed, other major FDA-approved AD drugs, such as cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and NMDA receptor antagonists (memantine), target synaptic receptors. However, the therapeutic effects of these available drugs are limited. A complete elucidation of synaptic pathology in AD will not only enhance our understanding of disease pathogenesis but also reveal new treatment strategies.

COMPTING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

J.C. and Y.W.Z. conceived the review and wrote the manuscript. All authors read and approved the final version of the manuscript.

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