Effect of Alzheimer's Disease on Synaptic Activity and Functional Connectivity

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ABSTRACT

Alzheimer's is a neurodegenerative disorder characterized by memory impairment and learning difficulties. Alzheimer's disease is recognized as the most common cause of memory loss and dementia in middle-aged and elderly individuals, and it is the fifth leading cause of death among the elderly. Extensive research is being conducted to identify the causes and pathological mechanisms involved in this disease, as a proper understanding of these mechanisms could lead to the discovery of fundamental treatments. In this article, we have looked at some of the pathological mechanisms of this disease, which result from changes in synaptic function and functional connectivity.

Keywords: Alzheimer's disease, learning, synaptic function, functional connectivity.

INTRODUCTION

In 1906, Dr. Alois Alzheimer discovered a specific disease while treating a 51-year-old patient with memory loss and presented its pathological aspects at the 37th Congress of German Psychiatrists. In 1910, his colleague, Dr. Kraepelin, named the disease "Alzheimer's disease" in his honor. Today, this disease is recognized as the cause of 50 to 75 percent of dementia cases in middle-aged and elderly individuals (1). Alzheimer's disease is an irreversible and progressive neurological disorder characterized by memory impairment, cognitive decline, changes in personality and behavior, dementia, and ultimately death (1,2). Symptoms of this disease include memory loss, learning difficulties, speech disorders, inability to recognize objects and people, and behavioral symptoms such as anxiety, restlessness, and in advanced stages, hallucinations and psychosis (3). Damage initially occurs in neurons involved in memory, language, and thinking (4), and it is believed that this damage begins 5 to 15 years before the onset of clinical symptoms and leads to death within 7 to 10 years after symptom onset (5,6).

In 2022, approximately 6.5 million Americans had Alzheimer's-type dementia, and this number is expected to reach 13.5 million by 2060 due to

the healthcare system's inability to prevent and treat the disease. In 2021 and 2022, Alzheimer's disease was the seventh leading cause of death in the overall U.S. population and the fifth leading cause of death among individuals aged 65 and older. Between 2000 and 2019, deaths from Alzheimer's increased by 145 percent (2,7,8).

Studies conducted in Iran in 2017 and 2019 revealed that the prevalence of dementia in the population over 65 years old is 2.3 percent, with 75 percent of these cases attributed to Alzheimer's disease. Given that Iran's population is aging and the likelihood of developing Alzheimer's increases with age, a significant rise in the number of individuals with Alzheimer's is anticipated (9,10).

Theories of Alzheimer's Disease

The accumulation of beta-amyloid plaques outside neurons and neurofibrillary tangles inside neurons are two significant changes in Alzheimer's disease that lead to neurodegeneration and a reduction in the number of neurons. Amyloid plaques disrupt inter-neuronal communication, while neurofibrillary tangles inside neurons impair intracellular function (5,11,12,13,14). Various theories have been proposed regarding Alzheimer's disease, including the amyloid hypothesis, inflammatory hypothesis, cholinergic hypothesis, calcium homeostasis and NMDA hypothesis, neurovascular hypothesis, metal ion hypothesis, lymphatic system hypothesis, and infectious hypothesis (1,15,16).

Disruption in Neurotransmitters Function

Studies have shown that Alzheimer's disease (AD) disrupts neural circuits at the neurotransmitter level. Most research highlights the dysfunction of cholinergic neurons in the basal forebrain, including the nucleus basalis of Meynert, the diagonal band of Broca, and the medial septal nucleus (MSN). These centers are the primary cholinergic output hubs of the basal forebrain to the cortex. Given the role of these areas in attention, alertness, and sleep, their dysfunction may relate to early disease symptoms. Tau protein accumulation along cholinergic inputs to the medial temporal structures and neocortex may explain memory impairment and subsequent executive function and personality disorders (20).

Glutamate neurotoxicity also plays a role in AD pathogenesis. Glutamatergic function via NMDA receptors is crucial for synaptic plasticity and neuron survival. However, excessive NMDA receptor activity leads to excitotoxicity due to pathological intracellular calcium increase, ultimately causing cell death and contributing to neurodegeneration in AD. Research indicates that beta-amyloid oligomers and tau can interact with several glutamate signaling proteins, such as NMDA receptors and proteins involved in glutamate uptake and recycling, leading to glutamate toxicity [18]. Factors affecting glutamatergic signaling include glutamate availability and NMDA receptor function regulation. The glutamate recycling and uptake system, which impacts glutamate availability, is impaired in AD. Additionally, reduced vesicular glutamate transporter (VGluT) capacity and expression, as well as selective loss of this transporter, have been observed in AD. It appears that Aβ disrupts glutamate uptake/recycling mechanisms, causing excessive glutamate levels. Besides high glutamate levels, NMDA signaling in AD may be increased through receptor modulation (18).

Compared to the well-documented deficits in cholinergic and glutamatergic systems, less research has been conducted on the role of the GABAergic system in Alzheimer's disease (AD). GABAergic neurotransmission also undergoes pathological changes in AD. In the temporal cortex of AD patients, GABA levels significantly decrease, indicating synaptic dysfunction and impaired neurotransmission. One study showed that GABAergic terminals in certain brain regions of AD patients and APP/PS1 transgenic mice, particularly in cortical neurons adjacent to amyloid plaques, were reduced, suggesting a loss of GABAergic neural function in AD. However, synaptic function changes in AD are more complex as disease progression continues. Activation of GABA receptors has been shown to increase tau phosphorylation, thereby increasing intracellular neurofibrillary tangles in neurons and contributing to AD development.

Maintaining a proper dynamic balance between the neurotransmitters glutamate and

GABA is essential for neural function. Synaptic balance alteration is a significant pathological factor contributing to AD development (19).

In some studies, the disruption of excitatory-inhibitory balance in the brains of Alzheimer's patients has been noted. One consequence of this imbalance can be the occurrence of seizures, which are observed in about 22% of Alzheimer's patients. In post-mortem AD temporal cortical tissue, markers indicating excitatory-inhibitory imbalance, including excitatory and inhibitory receptors, have been shown in Alzheimer's patients with and without seizures. This condition was worse in patients with seizures. In 5XFAD mice, the disruption of excitatory-inhibitory balance has been demonstrated from the prodromal stages to later symptomatic stages, which was associated with changes in the subunits of inhibitory and excitatory receptors (20).

Disruption of Synaptic Function

In Alzheimer's mice model, the accumulation of amyloid-beta (Aβ) leads to increased synaptic excitability, reduced firing of inhibitory neurons, and enhanced synaptic facilitation in the dentate gyrus and perforant path of the hippocampus. Additionally, there is impairment in both long-term and short-term potentiation in CA1 neurons of the hippocampus. In rodents with intraventricular injection of Aβ, long-term potentiation (LTP) is inhibited, resulting in the loss of synapses in the hippocampus. Studies have shown excessive neuronal excitability and an increase in the number of filopodia, indicating a possible compensatory mechanism for the reduction of synaptic inputs in the early stages of the disease.

Tau protein also plays a role in synaptic dysfunction. Electrophysiological and immunohistochemically studies in hippocampal slices have demonstrated impairments in synaptic plasticity, including reduced markers of neuronal activity, neuronal firing, synaptic density, and both short-term and long-term potentiation. Silencing tau expression before its accumulation has been shown to reverse these molecular disruptions and improve behavioral performance (12).

Disruption of Functional Connectivity

Researchers have suggested that Aβ and tau pathology leads to disruptions in brain network connectivity, including the default mode network (DMN). Damage to a specific brain region may cause dysfunction in its output, which in turn leads to impaired function and damage in connected areas. A particular network that is heavily regulated by cholinergic connections from the basal forebrain and is involved in Alzheimer's disease is the DMN. This network comprises a group of interconnected brain regions, including the medial prefrontal cortex, posterior cingulate cortex, inferior parietal cortex, lateral temporal cortex, and hippocampal formation. It is more active during rest and deactivates during many cognitive tasks. Dysfunction of this network, including its failure to deactivate during cognitive tasks, has been observed in Alzheimer's disease (17,21).

Electrophysiological studies have shown pathological "slowing" of neural activity in Alzheimer's patients in the temporal, parietal, cerebellar, and frontal cortices. Additionally, studies have reported increased low-frequency neural oscillations and decreased high-frequency oscillations (22). The reduction of fast oscillations (alpha, beta, and gamma frequencies) and the overall increase in slow rhythms (delta and theta frequencies) are the most common findings in resting-state EEG/MEG studies (23). Slowing of oscillations in the temporal and parietal cortices significantly impairs general cognitive function, attention, language, and processing speed (22).

Gamma oscillations are observed in many brain regions, including the neocortex, insula, striatum, olfactory bulb, thalamus, and other areas during wakefulness and sleep. The presence of GABAergic inhibitory interneurons, which are crucial for generating gamma oscillations, is a common feature of all these brain regions. Gamma activity contributes to a wide range of human cognitive functions, such as attention, perception, object recognition, memory processes, face recognition, and emotional paradigms, suggesting that gamma wave synchronization is an important process. Pathological increases in gamma band power are likely due to disruptions in GABAergic networks,

leading to an imbalance between excitation and inhibition in the central nervous system (23).

In Alzheimer's patients, a reduction in gamma power and synchronization at rest, along with an increase in gamma band power and cross-frequency coupling, has been observed. The increased power of cross-frequency coupling between beta/gamma bands and lower frequency bands in Alzheimer's patients reflects increased synchronization and may indicate a weakening of neural network complexity and the need to utilize more neural resources to maintain the brain's resting state (23).

Similar to the functional connectivity disruptions observed in human patients, Alzheimer's model mice with Aβ injection show reduced slow-wave activity in the cortex and decreased coherence between the hippocampus and the cortex, thalamus, and distant cortical areas. These findings confirm human results and demonstrate circuit dysfunction at structural, functional, electrophysiological, and neurotransmitter levels. These studies also indicate that circuit dysfunction may be alleviated by reducing Aβ and tau pathology (17,23).

Gotagni et al. (2013) demonstrated that a reduction in slow gamma activity (25 to 50 Hz) in the CA1 region of the hippocampus can lead to memory dysfunction. Evidence suggests that gamma activity decreases in Alzheimer's model mice, resulting in cognitive impairment (24).

Numerous studies have reported various issues in Alzheimer's model animals, including lower frequency of slow oscillations, reduced relative firing rate, and a shift of high-frequency oscillations towards lower frequencies (25), decreased overall brain oscillation power [26], abnormal theta oscillations and reduced theta/gamma cross-frequency coupling in the hippocampus (27), impaired gamma wave activity in the medial entorhinal cortex leading to memory dysfunction in Alzheimer's (28), reduced slow gamma band power, disrupted amplitude/phase coupling between the hippocampus and mPFC, weakened gamma oscillation synchronization (29), altered connectivity and separation of theta/gamma oscillations (30), abnormal delta and alpha oscillations (31), temporal and frequency disruptions in sharp wave-ripples (SWRs) due to reduced inhibitory control in the hippocampus (32), cortical hyperexcitability and increased hippocampal theta oscillations (33), and decreased synchronization between bilateral olfactory bulbs in theta, beta, and both low and high gamma frequencies (34).

CONCLUSION

Based on the numerous results mentioned in various studies, involvement at the level of synaptic function and consequently at the circuit level has been demonstrated. Considering these results, the effects of different treatments at this level can be taken into account. Additionally, there is hope for achieving significant results in treatments that focus on synaptic function and creating changes in functional connectivity.

Various therapeutic approaches have been developed based on the mechanisms discussed. Types of invasive and non-invasive brain stimulation, such as electrical and magnetic stimulation, are therapeutic approaches that can have various effects on cognitive functions such as memory and learning. The first possible therapeutic mechanism in these approaches is reversing the loss of synapses in memory circuits. Deep brain stimulation (DBS), an invasive method, applied to the entorhinal cortex reduces the damage to the synapses between neurons from layer II of the entorhinal cortex to CA1 of the hippocampus in Alzheimer's model mice. Additionally, applying deep brain electrical stimulation to the ventral diagonal band (VDB) significantly corrects the reduced density of cholinergic synapses in the dentate gyrus (36,37,38).

Brain stimulation holds the potential to reset the unstable state of neuronal oscillations in Alzheimer's disease, particularly theta oscillations in the hippocampus, and may thereby improve Alzheimer's symptoms. Disruption in theta wave activity leads to impairments in spatial memory and recognition, and restoring theta rhythm enhances learning abilities in mice. Deep brain stimulation resets the theta rhythm in the hippocampus, optimizes the encoding of incoming information, and improves memory performance in animal models [38,39]. Brain stimulation can also reset neural networks. Evidence suggests that the Papez circuit and the

default mode network are disrupted in Alzheimer's patients. Brain stimulation likely affects the upstream and downstream neural circuits related to the stimulation site, increasing functional connectivity between networks and consequently improving Alzheimer's symptoms (37,40).

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DECLARATION

Authors have no conflict of interest to declare.

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