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Review

Neuroplasticity and Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease that leads to a decline in cognitive function, including memory. The exact causes of AD are not fully understood, and to date no treatments are available that can stop the progression of this neurocognitive disorder. AD is associated with progressive loss of neurons, synaptic connectivity, and disruption of neuroplasticity in the brain. Neuroplasticity is the nervous system's ability to adapt and recover in response to experiences, injuries, or a pathological change. Synaptic dysfunction and impairment of neuroplasticity are important elements of AD progression and cognitive decline. Studies have demonstrated that enhancement of neuroplasticity effectively improves cognition and memory, preventing the progression of AD. In this narrative review, we discuss the role of various pathophysiological explanations regarding the impairment of neuroplasticity in the pathogenesis of AD. We also highlight neuromodulation approaches, such as exercise, neurotrophic factor mimetics, pharmacological drugs, light therapy, and diet therapy that can promote neuroplasticity and have the potential for use in the prevention and treatment of AD.

Keywords: Alzheimer's disease; neuroplasticity; cognitive function; neurotrophic factors

1. Introduction

Alzheimer's disease (AD), a neurodegenerative disease, is the most common form of dementia. AD presents with different and multiple clinical symptoms, mainly affecting cognitive domains. The early manifestation of AD is impairment in short-term memory. As the disease progresses, it affects attention, expressive speech, visuospatial processing, and executive functions [1,2]. AD gives rise to significant cognitive impairment and severely limits daily functioning, ultimately making patients dependent on family members or caregivers.

The exact cause of AD has not yet been fully uncovered, but it is characterized by the changes in the brain, including the accumulation of amyloid beta (Aβ) and neurofibrillary tangles (NFTs) of tau proteins in the brain. Nevertheless, several possible mechanisms, including neuroinflammation, mitochondrial dysfunction, dysregulation of neurotransmitter release, oxidative stress, and suppression of neurotrophic factors, are also involved in the disease process.

The amyloidogenic pathway of the cleavage of amyloid precursor protein (APP) forms neurotoxic Aβ [3]. The aggregation of neurotoxic Aβ peptides is an early pathology in AD, contributing to neurodegeneration, synaptic dysfunction, and neuronal loss [4]. In contrast, the anti-amyloidogenic pathway of APP cleavage releases soluble APPα (sAPPα), which prevents Aβ formation and has an important role in neuroplasticity [5,6]. While the classic hallmark of AD is said to be extracellular Aβ plaques, increasing evidence has shown that intracellular Aβ accumulation can play a role in the complex pathobiology of AD. Tau NFTs are intracellular in the AD brain. Tauopathies are related to neurodegeneration, synaptic dysfunction, and neuronal loss in the pathogenesis of AD [7]. The association between mutations of the microtubule-associated protein tau (*MAPT*) gene and tauopathies has been demonstrated [8]. The Apolipoprotein E4 (*ApoE4*) genotype is correlated with the build-up of Aβ and formation of NFTs, accompanied by neuroinflammation, neurodegeneration, and AD progression [9]. The expression of *APoE4* by astrocytes impairs the normal function of astrocytes alongside other glial cells, hence exacerbating Aβ and tau-related pathologies in AD, and promoting neurodegeneration and synaptic dysfunction. However, *APoE3* expression is asso-

ciated with a reduction in synaptic dysfunction and slower AD progression [10].

Neuroplasticity is characterized by the capability of the nervous system to adapt and recover, structurally and functionally, in response to novel experiences, injuries, or pathological changes [11]. On another reading, structural neuroplasticity refers to brain structural changes following learning and experiences, while functional neuroplasticity is the remodeling of synapses in response to brain injury or dysfunction. Neuroplasticity is a vital brain process that includes several mechanisms. It induces neurogenesis, synaptogenesis, and nerve sprouting through physiological and structural mechanisms that originate primarily at the cellular and molecular levels within synapses [12]. In this respect, synaptic dysfunction and impaired synaptic plasticity have emerged as principal contributors to the progression of AD and its associated cognitive decline [13].

Herein, we aim to review literature investigating neuroplasticity and its relevant mechanisms within the complex pathophysiology of AD. We also focus on the potential roles of neuroplasticity in the prevention and treatment of AD via pharmacological and non-pharmacological interventions.

2. Neuroplasticity

A basic explanation of neuroplasticity is initiated from the Hebbian plasticity theory, describing how synaptic connections are shaped, strengthened, and weakened [14]. Long-term potentiation (LTP) and long-term depression (LTD) are the two key elements of synaptic plasticity contributing to improved synaptic transmission and neuronal connections [15]. LTP and LTD are important for learning and memory. LTP is classically induced by repetitive high-frequency input, strengthening more efficient information flow, possibly through synaptic refinement, sprouting, and further synaptogenesis [16]. In contrast, LTD is typically associated with repetitive low-frequency input, which deteriorates the less efficient synaptic connections through synaptic pruning [17]. However, in recent years, the classic definition of LTP and LTD has changed. LTP and LTD are associated with the activation or reduction of glutamate receptors in the synapses, promoting a biochemical process in the postsynaptic terminals, and further enhancing the synaptic activity [18]. The excitatory neurotransmitter, glutamate, plays a role in synaptic plasticity. In most cases, both LTP and LTD induce their neuroplastic effects by N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors in synapses [19]. Following the induction of LTP, the Ca^{2+} influx through NMDA receptors (NMDARs) into the postsynaptic dendrite increases, further activating Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [20]. Subsequently, activated CaMKII translocates to the postsynaptic membrane and binds to the NMDAR subunit GluN2B, which forms the CaMKII-GluN2B complex [21]. This complex induces an autonomous activity of CaMKII that is not dependent on the Ca^{2+} level [21]. Thus, the CaMKII-GluN2B complex, in turn, results in the accumulation of AMPA receptors in the postsynaptic membrane, and consequently potentiates and maintains synaptic activity [22]. In contrast, during LTD, low levels of Ca^{2+} influx through NMDARs result in reduced synaptic activity and further synaptic pruning and spine shrinkage [23].

Synaptic loss and disruption of neuroplasticity are the hallmarks of AD [24]. Aβ is associated with the impairment of synaptic Ca^{2+} influx through NMDARs and suppression of LTP, subsequently enhancing synaptic dysfunction and dendritic spine loss [25]. Additionally, the accumulation of hyperphosphorylated tau proteins reduces the expression of NMDARs in synapses, which alleviates synaptic plasticity and, in turn, results in memory and cognitive dysfunction [26]. Regarding the potential role for LTP and LTD in association with the development of AD, understanding the multiple aspects of neuroplasticity is important. Moreover, mediating LTP and LTD could be an important therapeutic target for AD.

3. Neuroplasticity in Learning and Memory

Neuroplasticity plays an important role in learning and memory. Memories are encoded as spatio-temporal dynamic patterns of coordinated cellular activities of a neuronal engram, and the dynamics may be gradually altered to accommodate new information [27]. An engram is defined as a lasting physical change in the brain after an experience that leads to the storage of a memory [28]. In other words, an engram is the physical trace of the memory in the brain. It has been shown that silencing engram neurons prevents memory expression [29]. Neuronal representations are neural activities correlated with task-related stimuli, actions, and cognitive variables, while representational drift indicates ongoing changes in these representations [30]. It has been shown that the hippocampus facilitates learning and information recalling through two computational processes, which are known as pattern completion and pattern separation [31]. Pattern completion is a network's ability to respond to a degraded input pattern with the entire previously stored output pattern [32]. Pattern separation makes the stored representations of two similar input patterns more different, reducing the probability of errors in memory recall [32].

A study on male B6/129 F1 hybrid mice investigated the mechanism of altered plasticity following behavioral training [33]. It was tested in this study that alterations in intrinsic excitability, which are induced by learning, facilitate the encoding of new memories via metabotropic glutamate receptor (mGluR) activation. The hippocampal neurons showed increases in intrinsic excitability following learning, lasting for several days [33]. When animals were trained on a new task during this period, excitable neurons were reactivated, and memory formation depended on the activation of mGluRs rather than NMDARs. It was con-

cluded that increases in intrinsic excitability may serve as a metaplastic mechanism for memory formation [33].

4. The Effect of Aging on Neuroplasticity and AD

Aging is accompanied by memory decline [34], a reduction in attentional efficiency [35], and decreased task performance [36]. Age-related volume changes of the brain involve widespread white matter depletion [37] and region-specific gray matter changes, such as in the hippocampus [37,38], leading to ventricular enlargement. Since the normal cognitive function is generally associated with neuroplasticity, an age-related reduction of neuroplasticity may lead to cognitive decline [39]. Although the exact mechanism involved in this process is not fully known, a potential role for brain-derived neurotrophic factor (BDNF) has been suggested [40]. Aging negatively affects BDNF-involved cascades by reducing its gene transcription. Moreover, Other effects include disrupting BDNF protein synthesis and processing, along with desensitizing its receptor, tyrosine receptor kinase B (TrkB) [40].

The nicotinamide adenine dinucleotide (NAD)-dependent deacetylases, sirtuins, can regulate lifespan through inhibiting genomic instability and chromatin modification [41]. There is evidence about the anti-aging effects of sirtuins [42]. A study analyzed sirtuin1 [silent mating type information regulation 2 homolog 1 (*SIRT1*)] gene polymorphisms (rs7895833 A>G, rs7069102 C>G, and rs2273773 C>T) and their relation with levels of SIRT1 and other factors at different ages in healthy individuals [42]. A significant increase in the SIRT1 level in older people and a significant positive correlation between SIRT1 level and age in the overall studied population were observed. In addition, the oldest people carrying *AG* genotypes for rs7895833 had the highest SIRT1 level. This study suggested an association between the rs7895833 single nucleotide polymorphism (SNP) and lifespan longevity [42].

SIRT1 may be considered a predictive marker of AD in early stages [43]. Kumar *et al*. [43] evaluated the alterations in serum SIRT1 concentration in healthy individuals and patients with AD and mild cognitive impairment (MCI). A significant reduction in SIRT1 concentration was observed in patients with AD and MCI, compared to that in healthy elderly individuals. A previous study established a time point model for the clearance of Aβ in primary astrocytes [44]. The findings demonstrated that SIRT1 facilitates oligomeric Aβ degradation in primary astrocytes.

Furthermore, it has been shown that a reduction in SIRT1 and BDNF levels changes synaptic plasticity and neuronal excitability in older mice [45]. SIRT1 is also expressed in neurons of the hippocampus [46]. In a study using a combination of behavioral and electrophysiological paradigms, the effects of deficiency and overexpression of SIRT1 on mouse learning and memory and synaptic plasticity were assessed [46]. The results of the study showed cognitive abilities impairment in the condition of SIRT1 deficiency. It also has been found that the cognitive deficits in SIRT1 knock-out mice lead to defects in synaptic plasticity [46].

5. The Role of the Immune System in Neuroplasticity and AD

The immune system is involved in the regulation of memory, learning, neurogenesis, and neuroplasticity, predominantly mediated by inflammatory cytokines, neurotrophic factors, and glial cells [47].

Interleukin-1 beta (IL-1β) is a proinflammatory cytokine important in hippocampal-dependent memory and learning processes [48]. Goshen *et al*. [48] demonstrated the dual role of IL-1β in hippocampal memory formation in mice with transgenic overexpression of IL-1 receptor antagonist restricted to the central nervous system (CNS) (IL-1raTG), such that a slight increase in the hippocampal IL-1β levels promotes memory formation, whereas an excessive increase or blockade leads to memory impairment. Similarly, a significant elevation of IL-1β levels in the hippocampus reduces LTP, suggesting a potential mechanism for neuroplasticity disruption and Aβ formation in AD [49]. Balschun *et al*. [50] demonstrated that interleukin-6 (*IL-6*) gene expression in the hippocampus is increased during LTP, suggesting a counteracting effect of IL-6 at its physiological levels on neural plasticity and certain types of hippocampus-dependent learning and memory. They also observed a feedback interaction between IL-1 and IL-6 during hippocampal LTP, indicating that both interleukins are involved in memory consolidation.

Besides immune components, the glial cells, and astrocytes in particular, modulate synaptogenesis, neuroplasticity, learning, and memory [51]. Astrocytes are key elements of the regulation of neurotransmitter concentration in the synaptic cleft, modulating the release and removal of neurotransmitters in the tripartite synapses [52]. Tripartite synapses refer to the existence of bidirectional communication between neurons and astrocytes [53]. Through their signaling activity, astrocytes maintain and modulate the balance between excitatory and inhibitory synapses, thereby playing a role in the regulation of neuronal activity and synaptic plasticity [54]. In addition, astrocyte glycolysis provides support for the neuronal activity, positively contributing to neuroplasticity and cognitive function [55]. Regarding these studies, astrocytes contribute to synaptic transmission, remodeling, plasticity, and normal brain function. Consequently, impairment in their normal functioning may lead to complications in synaptic function and neuroplasticity.

Disruption of synaptic transmission and neuroplasticity is one of the hallmarks of AD and cognitive decline [56]. It has been shown that a disruption in the physiological function of astrocytes favors Aβ accumulation and

tau pathology, whereas an orchestrated function of astrocytes and microglia limits the progression of AD pathologies [57].

6. The Role of Mitochondria in Neuroplasticity and AD

Mitochondria are the main organelles involved in adenosine triphosphate (ATP) production, alongside the regulation of metabolism and apoptosis in cells. The cells' energy demands are primarily met by oxidative phosphorylation of sugar through the tricarboxylic acid cycle. Neurons are energy-intensive cells.

Aβ and tau pathologies can affect mitochondria in the brain. Aβ aggregation induces mitochondrial dysregulation of Ca^{2+} homeostasis, ultimately contributing to mitochondrial and synaptic dysfunction and neurodegeneration [58]. An APP/PS1 mouse model of AD revealed imbalances in the mitochondrial dynamics in the cerebral cortex and hippocampus [59]. Similarly, tau pathology is related to mitochondrial dysfunction, which finally impairs synaptic function and connectivity [60].

Mitochondria are plastic and dynamic organelles in the neurons. Mitochondria are capable of adaptation and remodeling to supply neuronal energy demands in response to different neuronal energy states. Such adaptation leads to structural and functional changes in mitochondria, which are involved in neuroplasticity and AD [61]. Mitochondrial dynamics occur in both pre- and post-synaptic neurons during synaptic transmission [62,63].

6.1 Mitochondrial Dynamics at the Presynaptic Terminals

Proper mitochondrial distribution and transport are important in providing support to synaptic transmission [64]. BDNF, through the activation of the TrkB receptor at the presynaptic terminal, increases the Ca^{2+} levels, halting mitochondrial transport, and induces presynaptic mitochondrial accumulation in the terminal axon [65]. This process promotes the stationary mitochondrial population and mitochondrial motility arrest, leading to the gathering of more mitochondria in the presynaptic area [65]. The effect of BDNF on mitochondrial halting promotes synaptic transmission, neurotransmitter release, and further neuroplasticity [65].

6.2 Mitochondrial Dynamics at the Postsynaptic Dendrites

LTP induces mitochondrial fission in the postsynaptic dendrites, an essential process in maintaining synaptic plasticity [62]. LTP, through the activation of postsynaptic NMDARS, increases the influx of Ca^{2+} into the postsynaptic neuron, which further enhances mitochondrial localization and fission at the postsynaptic dendrites [62]. Mitochondrial fission is mediated by dynamin-related protein 1 (Drp1), which is a key guanosine triphosphatase (GTPase) protein [66]. Eventually, as a result of this process, LTP, by inducing synaptic activity and further mitochondrial fission, results in synaptic plasticity [62]. In contrast, impaired mitochondrial fission possibly reduces dendritic mitochondrial fission, disrupting synaptic plasticity in the nervous system [62,67].

7. The Role of Neurotransmitters in Neuroplasticity and AD

7.1 Acetylcholine

Acetylcholine (ACh) is an important neurotransmitter associated with wakefulness, attention, learning, and memory. Nucleus basalis of meynert (NBM) is a structure that accommodates the basal forebrain cholinergic neurons (BFCNs). NBM has been identified as the primary and principal source of cholinergic innervation in the brain [68]. Tauopathy neurodegeneration of NBM is involved in neuronal loss and synaptic dysfunction of cholinergic innervation neurons, further leading to memory impairment and progression of AD [69]. Baskerville *et al*. [70] observed the effects of depleted ACh input from the NBM on cortical plasticity in young adult male rats. In this study, in the absence of ACh, no remarkable cortical plasticity was demonstrated. However, in the presence of ACh, notable enhancement of cortical and synaptic plasticity was detected.

7.2 Glutamate

Glutamate is the major excitatory neurotransmitter that mediates excitatory signal transmission on postsynaptic neurons, which is mediated through two important receptors, AMPA and NMDA receptors [19]. In AD, Aβ accumulation is linked to loss of the glutamatergic neurons and dysregulated levels of glutamate in the hippocampus [71]. Glutamate excitotoxicity has also been identified to enhance Aβ accumulation in AD, further contributing to neuronal loss, disruption of synaptic plasticity, and cognitive decline [72]. These preliminary findings indicate a potential reciprocal interaction between the glutamatergic system and Aβ accumulation, which exacerbates synaptic failure in AD [73].

7.3 Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS. Phosphorylated tau accumulation in GABAergic interneurons of the dentate gyrus of the hippocampus is related to disrupted hippocampal neurogenesis and cognitive decline in AD [74]. These findings indicate the important role of the GABAergic system in neurogenesis and synaptic plasticity, making it a therapeutic target for AD.

7.4 Norepinephrine

Norepinephrine (NE) or noradrenaline is implicated in modulating cognitive functions, including memory, attention, and arousal [75]. In AD, degeneration of the locus coeruleus (LC), the principal source of NE within the brain, is among the earliest pathological events [75,76].

Disruption of NE aggravates AD pathogenesis, including Aβ plaque formation and neuroinflammation [77]. Conversely, enhanced levels of NE can suppress inflammation along with improving cognitive function in animal models [77,78].

7.5 Dopamine

Dopamine (DA) is essential for movement, motivation, and memory [79]. The dopaminergic system is also affected in AD [80]. Using repetitive transcranial magnetic stimulation (rTMS) revealed impaired dopamine-modulated synaptic plasticity in AD patients [81]. The affected plasticity was possibly improved by a dopamine agonist [81]. Ventral tegmental area (VTA) dopaminergic neuron degeneration is related to impaired synaptic plasticity and memory decline in AD mice [82–84].

8. The Role of Neurotrophic Factors in Neuroplasticity and AD

8.1 Brain-Derived Neurotrophic Factor

BDNF is a key neurotrophic factor signaling via the TrkB receptor, which plays an important role in synaptic outgrowth and neuroplasticity [85]. Exercise and training have been identified to promote neurogenesis and neuroplasticity through the upregulation of neurotrophic factors such as BDNF [86]. Reduced levels of BDNF in the brain tissue samples of postmortem AD patients favor the AD pathology [87]. Decreased BDNF/TrkB signaling is associated with γ-secretase activity, Aβ accumulation, and tau hyperphosphorylation, leading in turn to neuronal loss and impairment of neuronal plasticity in AD [88].

8.2 Nerve Growth Factor

Nerve growth factor (NGF) is another key neurotrophic factor with a high affinity to TrkA and a low affinity to P75 neurotrophin receptors ($p75^{NTR}$). NGF modulates cholinergic neurons projected to the hippocampus to induce hippocampal LTP [89]. Dysfunction of the NGF signaling pathway in hippocampal neurons has been linked to the activation of the amyloidogenic pathway of APP and Aβ accumulation, which results in hippocampal neurotoxicity, neuronal loss, and neurodegeneration [90]. The loss of trophic support to the BFCNs due to dysregulation of NGFs and their receptors could be a potential explanation for the pathogenesis of neuronal loss in AD [91].

There is no curative treatment for AD. Approaches improving neuroplasticity can be potential therapies that could improve function or slow down cognitive decline in AD.

9. Pharmacological Interventions Inducing Neuroplasticity in AD

9.1 Donepezil

Donepezil is an acetylcholinesterase inhibitor medication that reduces the breakdown of ACh and increases ACh levels in the synapses, promoting cognitive function [92]. Donepezil has been shown to prevent Aβ-induced impairment of hippocampal LTP in a rat model and to reduce Aβ accumulation, demonstrating the neuroplastic effects in the treatment of AD [92].

9.2 Memantine

Memantine, an NMDAR antagonist, is also used to improve cognitive function in AD [93]. Caneus *et al*. [94] examined the effectiveness of several AD therapeutic drugs on an LTP system, a human-based platform that was designed to mimic the clinical manifestation of AD and also to serve as a screening system for monitoring responses to therapeutic agents. LTP was induced in mature human induced pluripotent stem cell (iPSC)-derived cortical neurons cultured on microelectrode arrays [94]. The authors concluded that Donepezil, Memantine, Saracatinib, and Rolipram can prevent Aβ-induced impairment of LTP and promote neuroplasticity in AD. Wang *et al*. [95] studied the role of Memantine on post-ischemic neurological recovery and neuroplasticity in a mouse model of stroke. They showed increased growth factors' concentration, such as BDNF levels, as well as enhanced neuroplasticity and neuronal remodeling.

9.3 Saracatinib

Nygaard *et al*. [96] performed a 4-week phase Ib randomized, double-blind, placebo-controlled clinical trial on 24 patients with mild to moderate AD to evaluate the safety, tolerability, and CNS availability of oral AZD0530 (Saracatinib), a Fyn kinase inhibitor. Findings suggested that Saracatinib is safe and well-tolerated in different doses and can be a potential therapeutic agent for AD. van Dyck *et al*. [97] conducted a phase IIa randomized clinical trial in 159 patients with mild AD to examine the efficacy, safety, and tolerability of Saracatinib. The authors observed that Saracatinib is generally safe and well-tolerated in patients with mild AD. Remarkable effects in AD treatment were not shown; however, they did not exclude the potential role of Saracatinib as a therapeutic agent for AD.

9.4 Rolipram

Cong *et al*. [98] studied the efficacy of Rolipram, a phosphodiesterase-4 (PDE-4) inhibitor, in the improvement of cognitive function and depression in 3xTg-AD mice. Behavioral tests related to learning, memory, anxiety, and depression were compared, and different neurochemical measurements were administered. The authors showed that Rolipram suppressed Aβ, NFTs, neuroinflammation, apoptosis, and neuronal loss. They also reveal that Rolipram can serve as a potential therapeutic agent for AD.

9.5 P021

P021 is a neurotrophic and neurogenic peptide mimetic compound that inhibits leukemia inhibitory factor

(LIF) signaling pathway and increases BDNF expression [85]. P021 reduces Aβ accumulation and tau hyperphosphorylation by mimicking the BDNF and enhancing its levels [99]. P021 demonstrated a promising therapeutic effect in the prevention of neuronal loss in AD [100].

9.6 LM11A-31

LM11A-31 is a small molecule that modulates $p75^{NTR}$ signaling and can prevent Aβ-related neurodegeneration, tauopathy, neuronal loss, and AD pathology [101]. Shanks *et al.* [102] conducted a 26-week randomized, placebo-controlled, double-blinded phase IIa clinical trial in 242 participants with mild to moderate AD to evaluate the efficacy of using LM11A-31 as a therapeutic target for AD. They concluded that LM11A-31 reduced the progression of AD pathogenesis; however, no remarkable active cognitive improvement was observed.

9.7 Sulforaphane

Zhang *et al.* [103] studied the efficacy of sulforaphane (SFN), a metabolite enriched in cruciferous vegetables, in the prevention of AD progression in an AD mouse model. Treatment with SFN was found to attenuate Aβ accumulation and cognitive decline, accompanied by upregulation of the $p75^{NTR}$. The authors observed that increased expression of $p75^{NTR}$ provides protective effects against AD and could be considered as a treatment option [103]. In a recent study, Khan *et al.* [104] further explored the potential role of SFN in a rat model of AD. They discovered that SFN reduced hippocampal Aβ aggregation, neuronal loss, and acetylcholinesterase activity. They also revealed that SFN improved memory impairment by its anti-inflammatory and neuroprotective effects. It was concluded that SFN could be a potential therapeutic agent for AD.

9.8 P75 Ectodomain

In a study by Yao *et al.* [105], P75 Ectodomain (P75ECD) was shown to be largely reduced in the CSF and the brain of the AD mice. Restoration of physiological levels of P75ECD via injection of adeno-associated virus (AAV)-P75ECD-Fc in the lateral ventricles of Aβ transgenic AD mice was associated with reversing the Aβ toxicity, tauopathy, and neuronal loss. Therefore, the authors suggest P75ECD as a novel therapeutic target for AD [105].

10. Non-Pharmacological Interventions Inducing Neuroplasticity in AD

10.1 Exercise

The beneficial effect of exercise on improving cognitive function has been well demonstrated [106,107]. Exercise improves cognitive function and neuroplasticity while enhancing BDNF immunoreactivity [108]. Following aerobic exercise, BDNF directly influences neuroplasticity by activating the Akt (protein kinase B) and cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) signaling pathways in the rat hippocampus [109]. A study on 3xTg-AD mice examined the effect of the intravenous injection of plasma extracted from the exercised mice on the improvement of hippocampus-dependent cognitive functions [110]. The results showed an improvement in mitochondrial function, neuroplasticity, and cognitive function, in addition to a suppression of apoptosis. A randomized controlled trial evaluated the effect of 6-month cycling on the cognition of AD patients using the AD assessment scale-cognitive subscale (ADAS-Cog) test, demonstrating a significant reduction in the scores, i.e., cognitive improvement, compared with the controls [111].

Nigam *et al.* [112] assessed the effect of exercise-induced upregulation of BDNF expression on AD pathogenesis. Their findings demonstrated that increased BDNF signaling, through enhanced α-secretase activity, leads to decreased Aβ levels, while sAPPα levels were increased in the samples. They suggest exercise upregulates BDNF, which in turn reduces the production of Aβ peptides by favoring the anti-amyloidogenic processing of APP [112].

In addition, it has been shown that exercise can increase SIRT1 expression levels [113]. Shi *et al.* [114] investigated the effects of 8 weeks of aerobic exercise, administration of chlorogenic acid, and a combination of both on Aβ deposition, inflammatory factors, oxidative stress markers, neuronal damage, and cognitive performance in the brains of AD model mice (APP/PS1). The results showed that aerobic exercise combined with chlorogenic acid activates the SIRT1/peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) signaling pathway and improves oxidative stress, neuroinflammation, Aβ deposition, and cognitive performance in mice [114].

10.2 Light Therapy

Light therapy has been suggested as a non-invasive and promising intervention for cognitive function and neuroprotection in AD, influencing through neuroplasticity mechanisms [115]. A study in an AD mouse model indicated that transcranial light therapy improved synaptic plasticity [115]. In this study, synaptic plasticity using electrophysiological parameters, including field excitatory postsynaptic potential (fEPSP), paired pulse facilitation (PPF), LTD, and LTP, was evaluated. The treated group showed higher levels of LTP than the control group. In another study using the 3xTg-AD mouse model, the combined effects of exercise with 40-Hz light flickering on cognitive function were investigated by evaluating the neuroinflammation, mitochondrial function, and neuroplasticity [116]. The results showed a significant decrease in Aβ, tau protein levels, and cell apoptosis, as well as a marked increase in mitochondrial function and synapse-related protein expressions. In a pilot, placebo-controlled clinical trial in dementia patients, the effect of 28 consecutive, six-minute transcranial sessions of near-infrared (NIR) stimulation using 1060–1080 nm light-emitting diodes was assessed

[117]. Findings demonstrated an improvement in executive functioning and a trend of improved electroencephalography (EEG) amplitude and connectivity measures in dementia patients. Another placebo-controlled clinical trial evaluated the effect of low-laser therapy with moderate-intensity aerobic exercise over 12 weeks in patients with anemia and mild cognitive dysfunction [118]. The results in both groups showed notable improvements in hemoglobin level, Montreal Cognitive Assessment Scale Basic (MoCA-B), Quality-of-Life for AD scale, and Berg balance scale scores. The experimental group showed more significant results compared to the control group [118].

10.3 Diet Therapy

The effect of a healthy diet on cognition has been demonstrated [119]. The results of a 4-year randomized controlled trial in 1401 men and women aged 57–78 years at baseline showed that a combination of moderate-intensity aerobic exercise and a healthy diet may improve cognition in older individuals [119]. In this regard, the role of SIRT1 has been considered [120]. The association between diet containing lipopolysaccharides/patulin and SIRT1 inactivation, cellular aging, and delayed hepatic Aβ clearance in diabetes and neurodegenerative diseases has been demonstrated [120].

10.4 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive method that generates a magnetic field over the scalp using a wired coil probe [121]. The magnetic field produces an electric impulse that travels down the skull directly to induce neuronal depolarization in the targeted brain region [121]. TMS can be used with low- or high-frequency stimulation modes to modulate LTP and LTD in the CNS [122]. Repetitive low-frequency TMS is associated with the weakening and inhibition of the synapses, resulting in LTD, while repetitive high-frequency TMS is related to the strengthening and excitation of the synapses, leading to LTP [122]. The LTP and LTD induced by rTMS can lead to neuroplasticity; however, the exact neurobiological mechanisms are not completely clear [122].

rTMS has been shown to promote synaptic plasticity and AD rehabilitation [123]. Findings suggest that rTMS enhances the efficiency of Aβ deposit clearance pathways in the brain, thereby reducing the aggregation and formation of Aβ, further promoting synaptic plasticity [123]. The rTMS also provides a frequency-dependent effect on the gene expression in astrocytes and glial cells, ultimately suppressing neuroinflammation, neurodegeneration, and neuronal loss [124]. In a study, rTMS was applied to the motor cortex of ischemic rats, which revealed upregulations in the expression of BDNF/TrkB signaling pathway, possibly contributing to synaptic plasticity, neurogenesis, and improved functional recovery [125]. The rTMS administration in a mouse model of AD was also associated with a decreased level of neuronal apoptosis and improved cognitive function [126]. Similarly, rTMS application in patients with mild to moderate AD revealed improvement in their cognitive and memory functions [127].

Regarding these findings, rTMS can enhance synaptic transmission, neurogenesis, and neuroplasticity in the neuronal network connection, thereby improving cognitive and memory function. However, the exact mechanism beyond the neuroplastic effects and cognitive improvements is not well-known.

10.5 Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is a neuromodulation technique applying electrical stimulation to the vagus nerve [128]. The surgical or invasive VNS (iVNS) was initially used to treat refractory epilepsy cases [128]. This method requires a VNS device to be implanted in the body for direct stimulation, which may follow surgical complications or device malfunction [129]. These challenges hampered the feasible use of iVNS in the routine management of nervous system disorders [129].

The non-invasive VNS method has similarly been used to modulate the nervous system activity, while preventing the invasive method complications [130]. The non-invasive VNS, clinically known as transcutaneous VNS (tVNS), provokes the auricular branch of the vagus nerve, Arnold's nerve, on the ear, or the cervical vagus nerve on the neck [130].

The tVNS exerts its effects through catecholamine release, especially NE from LC in response to afferent stimulation of the vagus nerve [131]. The NE released from the LC enhances the gene transcription of anti-inflammatory molecules and suppresses the proinflammatory cytokine signaling pathways in astrocytes and microglia [132]. Consequently, the anti-inflammatory effects induced by tVNS prevent neuroinflammation and neurodegeneration and further may favor neuroplasticity [133]. Besides its beneficial effects through the catecholamine release, VNS regulates the synaptic and memory function via the dopaminergic pathways [134]. The activation of LC causes dopamine release in the hippocampus, which modulates LTP, thereby enhancing synaptic transmission and memory [135].

Moreover, VNS has been identified to promote hippocampal phosphorylation of TrkB receptors and BDNF release, possibly promoting neuroplasticity and memory function in a rat brain [136]. Altogether, VNS may seem to be a promising neuromodulation technique for retaining cognitive function and memory in AD through enhancement of synaptic transmission and neuroplasticity [137].

Fig. 1 summarizes the potential therapeutic approaches contributing to the enhancement of synaptic plasticity and neurogenesis in AD.

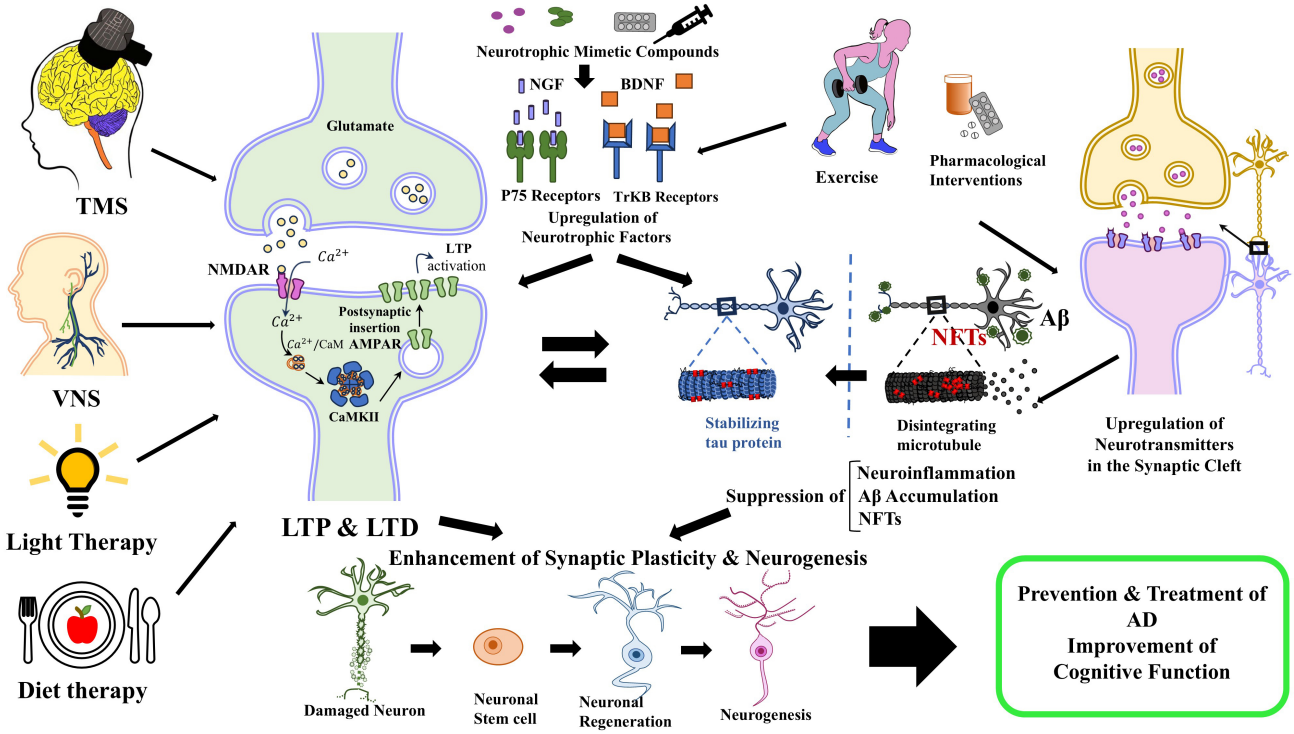

Fig. 1. The potential therapeutic approaches contributing to the enhancement of synaptic plasticity and neurogenesis in AD. Pharmacological interventions through upregulation of neurotransmitters and neurotrophic factors in the synaptic cleft, suppress the neuroinflammation, Aβ accumulation, and NFTs, alongside promoting LTP and LTD, can subsequently enhance neuroplasticity. Additionally, Exercise also increases the neurotrophic factors and ultimately promotes neuroplasticity. Non-pharmacological interventions, including light therapy, diet therapy, TMS, and VNS, other than exercise, may enhance the LTP and LTD, and further reduce Aβ accumulation, NFTs, and neuronal loss, possibly promoting neuroplasticity. Furthermore, there is a reciprocal relationship between LTP and LTD alongside suppression of neuroinflammation, Aβ, and NFTs, which both parts actively enhance each other's effects, further contributing to the enhancement of neuroplasticity. Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; LTP, long-term potentiation; LTD, long-term depression; NFTs, neurofibrillary tangles; NGF, nerve growth factor; NMDAR, N-methyl-D-aspartate receptor; TMS, transcranial magnetic stimulation; TrKB, tyrosine receptor kinase B; VNS, vagus nerve stimulation.

11. Conclusions

Cognitive decline in AD is associated with impairment of synaptic plasticity and neuroplasticity. Accumulation of Aβ and NFTs, immune system dysregulation, mitochondrial dysfunction, cholinergic, glutamatergic, GABAergic, noradrenergic, and dopaminergic system impairment, and defective release of neurotrophic factors such as BDNF and NGF contribute to neuronal and synaptic loss, leading in turn to impairment of neuroplasticity in AD. Pharmacological interventions, BDNF and NGF mimetics, exercise, light therapy, diet therapy, and neuromodulation approaches such as TMS and VNS, can be potential therapeutic interventions that may affect neuroplasticity in AD. These approaches can promote neuroplasticity and offer complementary benefits in the prevention and treatment of AD, as well as the improvement of cognitive function. Preclinical and clinical investigations are suggested to further elaborate on the fundamental molecular and cellular processes regarding the role of neuroplasticity in the progression, prevention, and treatment of AD. Future studies can focus on the interventions inducing neuroplasticity, such as neurotrophic factor mimetics, pharmacological interventions, and neuromodulation strategies, which represent promising therapeutic potential in AD.

Author Contributions

SA had the idea for the narrative review article. All authors contributed to the literature search of the article. AAG and SGS drafted the article. SSK, FK, SG, MB, and SA critically reviewed and revised the article. SG drew the figure. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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