Heliyon 10 (2024) e39217

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Unveiling the multifaceted pathogenesis and therapeutic drugs of Alzheimer's disease: A comprehensive review

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ARTICLE INFO

Keywords:
Alzheimer's disease
Aβ deposition
Tau protein phosphorylation
Cholinergic dysfunction
Neuroinflammation
Mitochondrial oxidative stress
Ferroptosis
Gut microbiota
miRNA
Therapeutic drugs

ABSTRACT

Alzheimer's disease (AD) is a severe neurodegenerative disorder characterized by the accumulation of β-amyloid (Aβ) plaques and tau phosphorylation-induced neurofibrillary tangles. This review comprehensively summarizes AD pathogenesis and related factors, drawing on a wealth of authoritative reports and research findings. Specifically, we delve into the intricate mechanisms underlying AD pathology, including Aβ deposition, tau protein phosphorylation, cholinergic dysfunction, neuroinflammation, mitochondrial oxidative stress, ferroptosis, imbalance in the gut microbiota, and microRNA dysregulation. We also explored the effects of these factors on the brain, including synaptic damage and cognitive impairment. Moreover, our review highlights the associations between the pathogenesis of AD and inflammatory cytokines in the peripheral blood and cerebrospinal fluid, dysbiosis of the gut microbiota, and changes in microRNA expression. Overall, we provided a systematic and illustrative overview of the pathogenesis and therapeutic drugs for AD, offering help in the prevention and treatment of this condition.

1. Introduction

With global economic and medical advancements, population aging is becoming increasingly evident, making dementia in older adults a significant challenge. Among the various types of dementia, Alzheimer's disease (AD) is the most prevalent. The hallmark features in patients with AD are β-amyloid (Aβ) deposition, neurofibrillary tangles (NFTs), and the loss of neurons and synapses in the brain. The 2018 World Health Organization (WHO) report on AD highlights the global crisis posed by dementia, estimating 50 million patients worldwide in 2018. Projections indicate that this number will continue to rise, reaching 82 million by 2030, imposing a significant healthcare burden on a global scale [1]. Consequently, an increasing number of researchers are investigating the etiological mechanisms of AD [2]. AD is named after Alois Alzheimer, the neurologist who first discoverd it [3]. His discovery paved the way for further research into the pathogenesis of AD, with the initial identification of Aβ plaques as a contributing factor [4]. Subsequently,

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https://doi.org/10.1016/j.heliyon.2024.e39217
Received 31 March 2024; Received in revised form 2 August 2024; Accepted 9 October 2024
Available online 11 October 2024

Iqbal et al. isolated NFTs from the brains of patients with AD [5]. As research has progressed, an increasing number of hypotheses regarding AD have been proposed. Extensive research has revealed that the pathogenesis of AD is associated with Aβ deposition [6], tau protein phosphorylation [7], cholinergic dysfunction [8], neuroinflammation [9], mitochondrial oxidative stress [10], ferroptosis [11], an imbalance in the gut microbiota [12], and alterations in microRNA (miRNA) expression [6]. These factors can interact with and exacerbate each other, further accelerating AD progression. This review aims to organize the multiple mechanisms and medications for AD to provide insights into its prevention and treatment.

2. Molecular mechanisms of AD

2.1. Aβ

There are two hallmark pathological features in the periphery of hippocampal neurons in patients with AD, one of which is Aβ deposition, primarily formed by smaller fragments of amyloid precursor protein (APP). APP generates Aβ peptides of different lengths after successively undergoing β-secretase and γ-secretase [13]. Aβ1-40 and Aβ1-42 are particularly neurotoxic and are frequently associated with AD [14]. The in-depth understanding of the process of secretase-induced Aβ formation and the mechanism of Aβ damage to neurons provides more theoretical basis for the future development of Aβ-targeted drugs for the treatment of AD.

2.1.1. Role of secretory enzymes on Aβ formation

β-secretase 1 (BACE1), an aspartyl protease predominantly found in brain neurons, is known for cleaving APP to produce Aβ [13,15]. Scientists have studied BACE1 in various aspects, including the genes that regulate BACE1 and its post-translational modifications [16]. Bao et al. found that both the activity and stability of BACE1 were enhanced following SUMOylation at residue K501 [17]. The stability-enhanced BACE1 is not easily degraded by the lysosome, which can promote APP shearing, leading to Aβ accumulation [17]. BACE2, which shares 64 % amino acid similarity with BACE1, is predominantly expressed in peripheral tissues [18,19]. However, its level is increased in the brains of patients with AD and has been regarded as a marker that is highly correlated with AD. Moreover, the

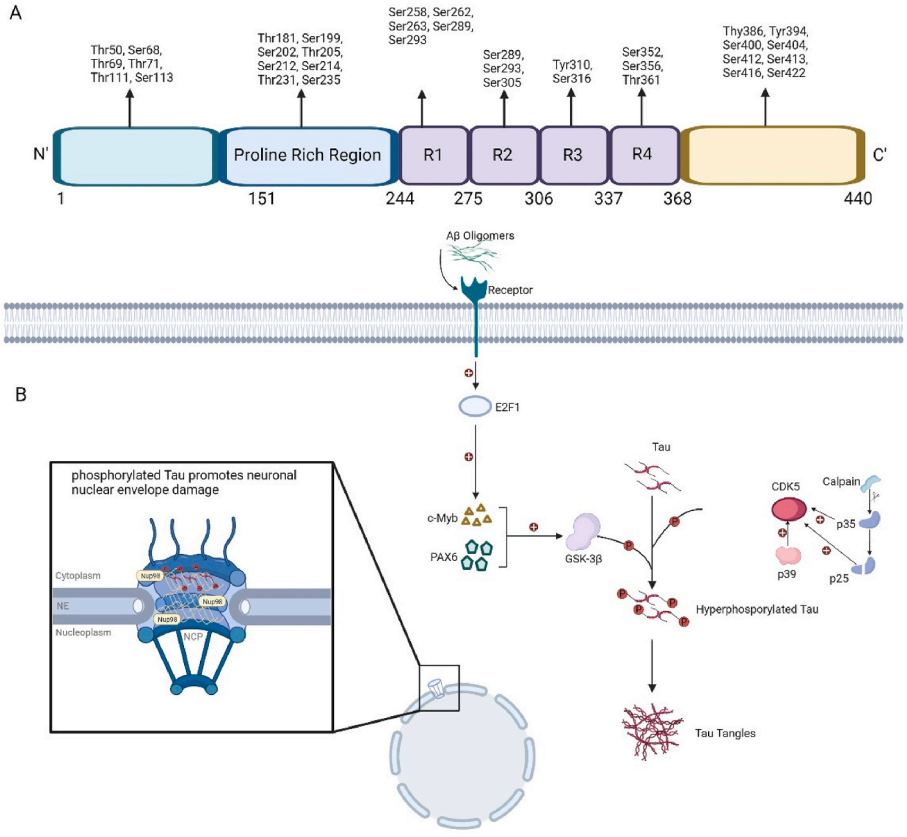

Fig. 1. Tau phosphorylated sites and related kinases. (A) The adult full-length tau protein has 85 potential phosphorylation sites, including 45 serine, 35 threonine, and 5 tyrosine residues. The phosphorylation sites shown in the figure are associated with the development of AD. (B) Aβ oligomers bind to the receptor, which then upregulates E2F1. This, in turn, induces the expression of PAX6 and c-Myb. PAX6 and c-Myb can directly regulate the transcription of GSK-3β, thereby promoting tau phosphorylation. CDK5 also promotes tau phosphorylation, and CDK5 is regulated by p35, p39, and p25. In addition, tau interacts with Nup98, leading to defects in nucleocytoplasmic transport.

amount and activity of BACE2 are related to BACE1 levels in the brain [20]. Thus, BACE2 was initially assumed to have a similar function to BACE1 in cleaving APP at the β-site to produce Aβ. However, later research questioned this idea and proposed that BACE2 may play a protective role for neurons [21,22]. Evidence indicates that elevated levels of BACE2 do not exacerbate the deposition of Aβ40 and Aβ42 but rather reduce them [23]. However, Wang Z et al. has found that under specific conditions, BACE2 is able to cleave APP at the β-site [2]. Hence, scientists hold different views on the role of BACE2 in Aβ formation and AD processes. We are currently unable to clearly determine whether BACE2 promotes or inhibits the production of Aβ, possibly due to varying experimental conditions. Therefore, its specific mechanism of action remains to be studied.

2.1.2. Aβ is aggressive to nerve cells

Research suggests that Aβ impairs neuronal cell function and reduces cell viability through multiple pathways.

Shankar et al. revealed that Aβ oligomers impaired learning and memory abilities in rats [24]. Evidence indicates that Aβ oligomers significantly increased long-term depression, and the density of dendritic spines was decreased around the rodent hippocampus [24]. Clinical trials revealed that removing amyloid plaques does not improve symptoms of AD, whereas inhibiting Aβ oligomers resulted in better clinical outcomes, so Aβ oligomers are considered the more neurotoxic forms [25]. Moreover, Aβ oligomers are duplicated in astrocytes over time and induce neural damage [26]. Teng et al. discovered that the number of the C-terminal fragment of the synaptic adhesion protein N-cadherin amplifies the synaptotoxic effects of Aβ [27]. Furthermore, a delay in synaptic vesicle endocytosis promotes the binding of Aβ oligomers to synaptic vesicle membranes and facilitates their internalization, resulting in synaptic impairment. Aβ not only affects hippocampal neurons but also causes injury to microglia. Microglia are mononuclear macrophages of the central nervous system (CNS) that relate to the growth and development of neuronal cells [24]. Baron has found that the microglia surrounding the Aβ acquired the specifically activated phenotype, accompanied by a light increase in cytokines [25]. Additionally, Liu Q et al. discovered that Aβ aggregates up-regulate the expression and function of α7 nicotinic acetylcholine receptor (nAChR), leading to decreased cell viability [23].

2.2. Tau phosphorylation

Tau-phosphorylated proteins, commonly found in the mammalian brain, are primarily located in axons, and regulate axonal transport [28]. The C-terminal domain of tau comprises four repeating regions: R1, R2, R3, and R4 [29]. Phosphorylated tau (p-tau) is a key factor in the formation of NFTs. We examined both the phosphorylation sites of tau and the effects of p-tau on neuronal structure and function to understand the role of phosphorylated tau in AD pathogenesis.

2.2.1. Tau phosphorylated sites involved in AD

Tau protein has 85 sites potentially linked to phosphorylation [30]. At these sites, approximately 40 residues are phosphorylated, which are considered high-risk factors for AD [31].

Aberrant phosphorylation of Ser289 and Ser293 significantly destabilizes microtubules and promotes tau accumulation by inducing structural changes in the monomeric R2 peptides (Fig. 1A) [30]. In the monomer, Ser289 phosphorylation enhances ordered-disordered structural transitions and intramolecular interactions, resulting in a more compact phosphorylated R2. In contrast, in dimers, phosphorylation of Ser289 promotes β-fold formation, which can lead to the oligomerization of R2 peptides. Oligomerization of tau during aggregation is the most neurotoxic form, inducing neuroinflammatory factors, binding to astrocytes and microglia, and triggering apoptosis [32].

Furthermore, a lot of tau phosphorylation sites involved in AD, including Ser199, Ser214, and Ser231, are reported (Fig. 1A) [33–36]. However, our current understanding of these sites is limited by their association with tau phosphorylation, and investigating their upstream and downstream mechanisms and interactions poses challenges for future research.

2.2.2. Kinase promoting tau phosphorylation

Phosphorylation of tau relies on the action of phosphorylases, and an in-depth examination of the function of phosphorylases contributes to a further understanding of the pathogenesis of AD and provides a crucial theoretical basis for targeting p-tau for the treatment of AD.

Glycogen synthase kinase-3β (GSK-3β) is an important phosphorylating enzyme that affects axonal transport function and rapidly inhibits mitochondrial and neurotrophic factor receptor TrkA movement [37,38]. Moreover, Singh T et al. revealed that tau proteins need to be preprocessed by CDK-5 before GSK-3β [39]. Additionally, Aβ can enhance tau phosphorylation by mediating GSK-3β and CDK-5, particularly GSK-3β (Fig. 1B). Recent findings by Yalun Zhang suggest that the upstream pathway leading to GSK-3β-induced tau phosphorylation is regulated by multiple factors [40]. Aβ upregulates E2F1, which in turn induces the expression of PAX6 and c-Myb. Both PAX6 and c-Myb are direct targets of E2F1 (Fig. 1B). PAX6 directly regulates GSK-3β transcription and induces tau phosphorylation at Ser356, Ser396, and Ser404 [40].

2.2.3. P-tau promotes neuronal nuclear envelope damage

While the sites and kinases associated with tau phosphorylation are known, the mechanism through which p-tau damages neurons and induces AD remains unclear. The nuclear envelope (NE) is vital for maintaining a stable nuclear environment. The nuclear pore complex, located on the NE, facilitates the exchange of materials and information between the cytoplasm and nucleus (Fig. 1B). Lisa Diez et al. suggests that the accumulation of p-tau near the neuronal NE impairs the transport of substances within and outside the nucleus [41]. Further research has demonstrated that tau interacts with phenylalanine-glycine (FG)-rich nucleoporins 98 (Nup98),

forming aggregates in the nuclear pores and obstructing material exchange [41]. Impaired transport of substances within the nucleus may contribute to cellular dysfunction and death, which are closely associated with AD [42].

3. Systemic factors in AD

3.1. Cholinergic dysfunction

Acetylcholine (ACh), the first neurotransmitter discovered in humans, is crucial for neuronal function. The cholinergic hypothesis suggests that cognitive impairment causes the destruction of cholinergic neurons. Cholinergic neurons participate in various physiological functions of the brain, including attention and memory [43]. Three key factors affect the action of ACh: (1) its synthesis; (2) binding of ACh to its receptor; and (3) degradation of ACh by acetylcholinesterase (AChE).

3.1.1. ACh synthesis disorder

In cholinergic neuronal terminals, ACh is formed from choline and acetyl coenzyme A (acetyl-CoA) by the enzyme choline acetyltransferase (ChAT) (Fig. 2) and plays an important role in transporting information between reportors [44]. ACh is a product of the pyruvate produced during the tricarboxylic acid (TCA) cycle. However, the deposition of Aβ significantly reduces the efficiency of pyruvate participation in the TCA cycle [45], leading to decreased production of ACh and ATP. Excess glutamate causes postsynaptic Ca^{2+}, activating pyruvate dehydrogenase kinase, which inhibits pyruvate dehydrogenase complex and compromises mitochondrial

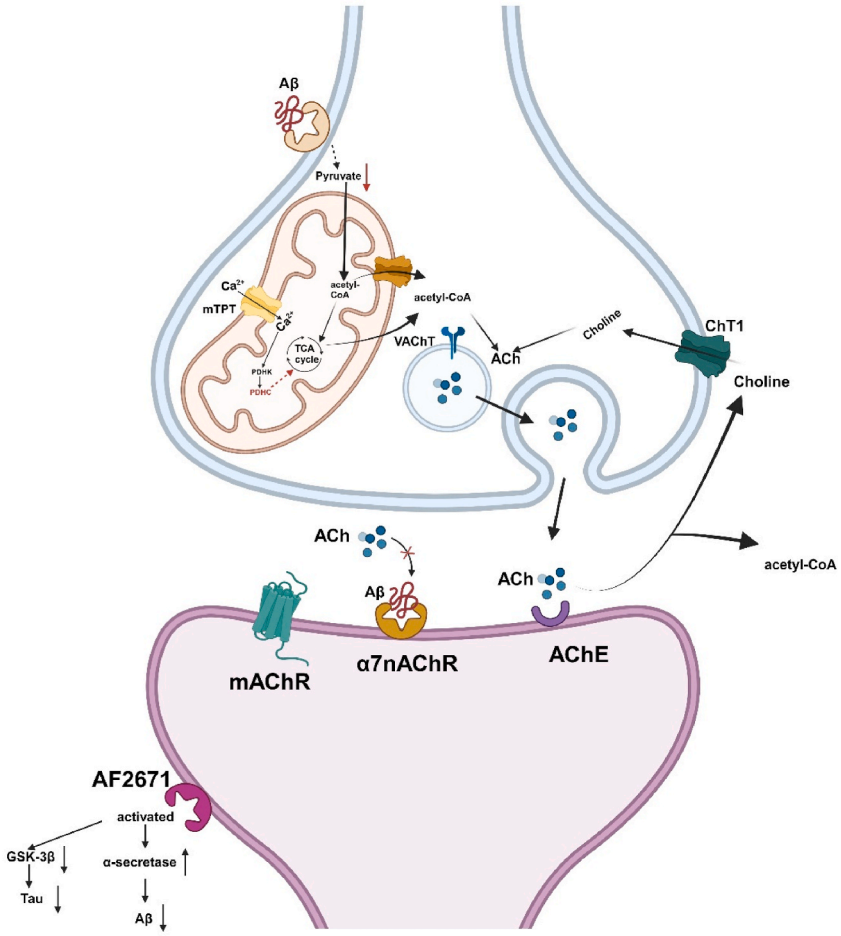

Fig. 2. ACh plays an important role in the nervous system and influences memory and recognition. **(1)** Synthesis of ACh. Acetyl-CoA and choline are the raw materials for the synthesis of ACh, and most of the ACh comes from the TCA cycle. However, Aβ reduces pyruvate utilization, thus leading to a reduction in ACh production during the TCA cycle. Ca^{2+} overload can activate pyruvate dehydrogenase kinase (PDHK), which inhibits pyruvate dehydrogenase complex (PDHC) and ultimately affects the TCA cycle and production of ACh. **(2)** Receptors for ACh. ACh is transported out of the axonal region by VAChT and then combined with muscarinic or nicotinic receptors. This process plays an important role in information transfer. However, Aβ binds α7nAChR, thereby reducing ACh binding to α7nAChR. AF2671 (M1 mAChR) increased α-secretase and decreased Aβ synthesis. Meanwhile, AF2671 decreased the level of tau by inhibiting the activation of GSK-3β. (Image created using Biorender.com.)

activity [46,47]. According to the cholinergic hypothesis, cognitive decline in patients with AD is the result of a combination of ACh and ATP deficiencies.

3.1.2. Impaired ACh receptor function and impaired transport

ACh activates two types of receptors: muscarinic and nicotinic. Among the five known isoforms of muscarinic ACh receptors (mAChRs), M1 mAChR has the highest distribution in the CNS and is involved in numerous brain activities [48,49]. Stimulation of AF267B (an M1 mAChR agonist) increases α-secretase activity and decreases Aβ synthesis [50,51]. Additionally, stimulation of AF267B inhibits GSK-3β activity, resulting in reduced tau levels. These studies suggest that the activation state of M1 mAChR affects brain cognitive functions by regulating Aβ and tau. The neuronal nAChR consists of α and β subunits, which combine to form a pentameric receptor complex [52]. In the CNS, most nicotinic receptors are expressed on the membranes of presynaptic neurons, and their main role is to regulate the release of neurotransmitters [43,53–55] such as glutamate, GABA, dopamine, 5-hydroxytryptamine, norepinephrine, and ACh [56–61]. Moreover, Aβ demonstrates a strong affinity for α7nAChRs [62], which results in compromised ACh transport. In addition, Aβ interacts with cholinergic components in various ways, including impairing cholinergic function, inhibiting the activity of ChAT and ACh, and increasing AChE activity [63]. Aβ and p-tau can not only directly damage neurons but also indirectly impair neuronal function by disrupting the cholinergic system.

3.2. Neuroinflammation

Neuroinflammation is the inflammation of the CNS, which is regulated by the involvement of neuroglia, including microglia and astrocytes [9]. The activation of microglia and astrocytes contributes to neuronal growth, development, and repair; however, prolonged activation induces neuroinflammation, impairs the ability of glial cells to clear amyloids, and exacerbates neurodegenerative diseases.

3.2.1. Microglia-related neuroinflammation

Microglia, the brain's innate immune cells [64] and about 10 % of the cells in the nervous system [65]. Microglia are divided into resting (M0) and activated (M1 and M2) states and play different roles in the brain. M0 microglia are highly branched, constantly moving through synaptic stretches, and act as the CNS [66]. After being activated by pathogens and Aβ, M0 microglia differentiate through the regulation of damage-associated molecular patterns or pathogen-associated molecular patterns [67,68]. M1 microglia, activated by Toll-like receptors or interferon-gamma, lead to neuronal damage and impaired phagocytosis through the production of large amounts of NO, reactive oxygen species (ROS), interleukin (IL)-1β, IL-6, IL-18, and TNF-α [69,70]. In contrast, M2 microglia is activated by IL-4 or IL-13, which exerts reparative effects and phagocytosis by releasing anti-inflammatory factors, including transforming growth factor-β, IL-4, IL-10, and IL-13 [69,70]. However, the M1/M2 phenotypic nomenclature is not widely recognized, mainly because it crudely divides microglia into two types.

Recent studies have revealed that the microglial activation phenotype extends far beyond the M1/M2 phenotype. Analysis of all immune cells ($CD45^{+}$) derived from the brains of 5XFAD mice using massive parallel single-cell RNA-seq revealed two clusters of microglia expressing unique genes, including apolipoprotein E (ApoE), lipoprotein lipase, and Cystatin F, and defined microglia as disease-associated microglia (DAM) [71]. DAM aggregates near Aβ and exhibits phagocytic activity [71]. To date, a variety of microglia surface receptors have been found to interact with Aβ, including scavenger receptors, TLR, CD36, RAGE, TREM 2, and late glycosylation end product receptors [72,73]. In addition to classical HLA-DR upregulation, recently identified microglia activation markers include F4/80, CD68, CD45, and ionized calcium-binding adapter molecule 1 [66,74].

3.2.2. Astrocytes-related neuroinflammation

Astrocytes are involved in the regulation of blood-brain barrier (BBB) stability, secretion of neurotrophic factors, and modulation of synaptic function and plasticity [66,75], and play an important role in the maintenance of homeostasis in the CNS. Astrocytes stimulated by pathogens or Aβ can develop two phenotypes with completely opposite activation states, the neurotoxic A1 phenotype (A1 astrocytes) and the neuroprotective A2 phenotype (A2 astrocytes) [76–78]. Activated microglia induce A1 astrocytes by IL-1α, TNF, and C1q, resulting in the loss of the ability of A1 astrocytes to promote neuronal survival, growth, synaptogenesis, and phagocytosis [79]. In the brain of patients with AD, A1 astrocytes highly express glial cell acidic protein, S100 calcium-binding protein B (S100B), and complement C3 (C3) [78]. S100B is a cytokine that activates cyclooxygenase-2 in microglia by upregulating nitric oxide synthase, ultimately leading to neuronal death [64]. Astrocytes extensively release inflammatory cytokines, including IL-1, IL-6, and TNF-α, when activated by pathogens or Aβ, which can have beneficial or harmful consequences [80]. Additionally, since astrocytes express BACE and presenilin-1, cytokine stimulation may induce Aβ production in astrocytes [64].

In AD, astrocytes that specifically express ApoE are thought to have a role in degrading Aβ [81]. A variety of receptors exist on the surface of astrocytes that can bind to Aβ, including the receptor for advanced glycosylation end products, lipoprotein receptor-associated proteins, membrane-associated proteoglycans, and scavenger receptor-like receptors [82,83]. Therefore, we know that the phagocytosis of glial cells is very important for the protection of the CNS.

3.3. Mitochondrial oxidative stress

Mitochondria produce ATP through oxidative phosphorylation (OXPHOS), which plays a key role in maintaining endogenous neuroprotective and repair mechanisms [84]. However, with age, mitochondria accumulate oxidative damage, leading to

neurodegeneration, impaired synaptic plasticity, and associated cognitive deficits [84]. An in-depth investigation of the relationship between mitochondrial functional impairment and neurons can help further understand AD pathogenesis and provide a more comprehensive theoretical basis for the future development of AD therapeutic drugs.

The severe imbalance between ROS and reactive nitrogen species production and oxidative stress induces antioxidant defenses, which are significantly increased in the brains of patients with AD and occur earlier than Aβ accumulation [85]. The cell membrane contains more unsaturated fatty acids, whereas the catalase content of neurons is low; therefore, the brain is more prone to oxidative damage [86,87]. Recently, studies have shown that Aβ can insert into cellular membranes, leading to the generation of ROS and the occurrence of lipid peroxidation in the membranes [10,88]. Even Aβ aggregation at the mitochondrial membrane disrupts mitochondrial transport, leading to a decrease in OXPHOS enzyme activity and a decrease in the transmembrane electrochemical gradient, which impairs mitochondrial function and increases ROS levels [89,90]. In tau-knockout mice, ROS are significantly reduced, mitochondrial fusion is increased, mitochondrial permeability transition pore and cyclophilin D is inhibited, and ATP production is increased, suggesting that tau overexpression can cause aberrant mitochondrial fusion and oxidative stress [91,92]. Tau inhibits the binding of dynamin-related protein 1 to mitochondria by binding to the actin cytoskeleton, resulting in mitochondrial elongation and increased fusion [86]. Mitochondria provide energy to support membrane ion exchange and synaptic transmission, and maintain Ca^{2+} homeostasis [86,90]. When mitochondria take up excess Ca^{2+}, it impairs mitochondrial function, leading to elevated ROS levels, inducing Aβ deposition and tau phosphorylation, further damaging neurons [93].

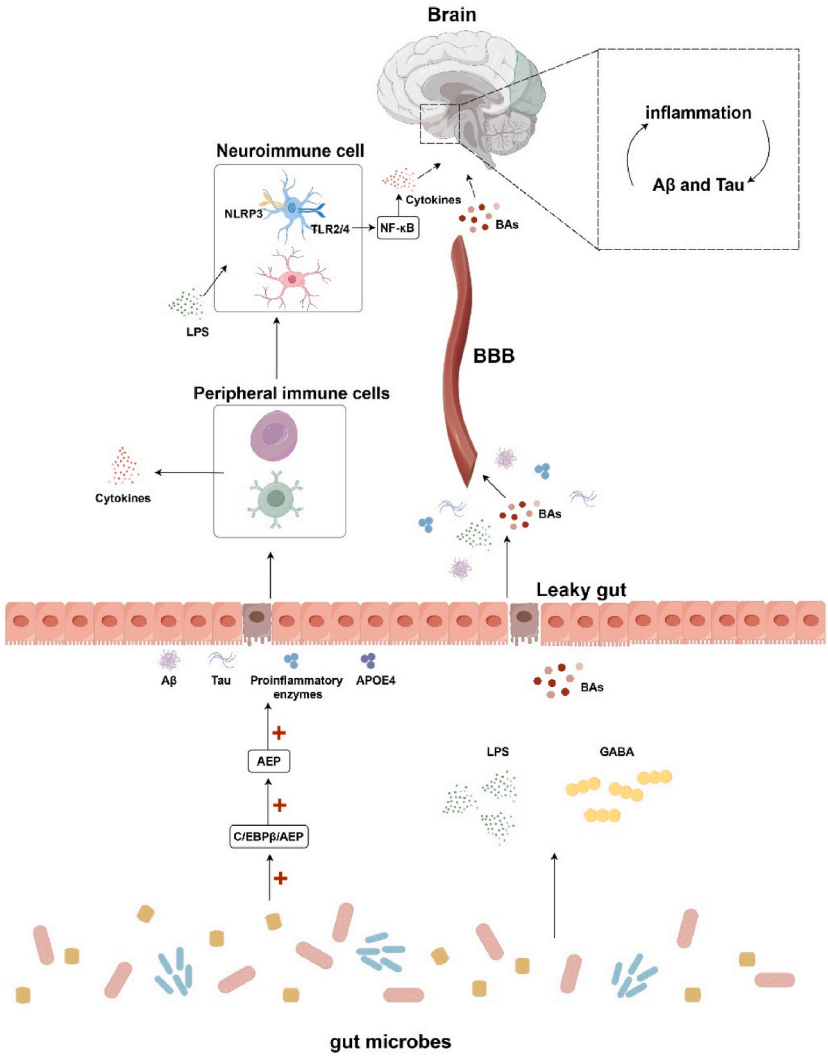

Fig. 3. Gut microbes activate C/EBPβ/AEP signaling, elevating pro-inflammatory enzymes and resulting in increasing levels of APOE4, APP, Aβ, and Tau. These metabolites can be released from the intestinal epithelium into the peripheral bloodstream. exacerbating the inflammatory response, including neuroinflammation. Bile acids may increase BBB permeability and allow intestinal metabolites to enter the CNS, leading to inflammation and AD. (Image created using Figdraw).

3.4. Ferroptosis

Iron is a trace element in the body that is involved in the regulation of many physiological activities. Fe^{3+} and Fe^{2+} are storage and transport forms, respectively, in the CNS. However, under conditions of iron overload or excessive free iron, the equilibrium of the antioxidant system is disrupted [94,95], leading to oxidative stress and neuronal cell death [96,97].

Normally, ferroportin 1 acts as a remote regulator of intracellular iron homeostasis and transports excess ferritin outside the cells [98]. However, nuclear receptor coactivator 4 degrades ferritin to free iron, and excessive intracellular iron accumulation can lead to elevated ROS levels and oxidative stress, promoting cellular ferroptosis [98,99], leading to neuronal cell damage. Iron transporter protein 1 (Fpn-1) is the only known non-heme iron transporter protein in mammals [100]. Its primary function is to regulate systemic iron homeostasis by binding to transferrin and transporting iron to iron-demanding tissues. Bao observed morphological and molecular features indicative of ferroptosis in $Fpn^{fl/fl/NEXcre}$ and AD mice [100]. Fpn deficiency in the hippocampus is accompanied by AD-like phenomena, including brain atrophy and memory deficits.

NADPH oxidase 4 is a major source of ROS and induces ferroptosis by impairing mitochondrial function in astrocytes [101]. Philip et al. found that white matter-degenerating microglia are enriched in the iron-binding protein light chain ferritin, which accumulates lipid droplets and undergoes peroxidative damage [102]. GPX4 is indispensable for the reduction of H_2O_2 and is the only enzyme capable of reducing phospholipid hydroperoxides. The loss of GPX4 activity is an important cause of lipid peroxide formation and accelerates ROS production, ultimately inducing ferroptosis in cells [103,104]. Recent research suggests that ferroptosis is not independently involved in the pathological response to AD; it also forms a complex network of linkages with p-tau to participate in AD. This can occur via Cys-Cys binding or hyperphosphorylation of tau proteins via the kinase pathway and ferroptosis [105].

The concept of ferroptosis was first introduced 10 years ago by Dr. Brent R. Stockwell and is related to the development of diverse diseases, including AD. However, ferroptosis remains a relatively new area of research, and its study in the context of AD has a large scope.

3.5. Imbalance of intestinal flora

The human gut contains 10–100 trillion commensal microbial cells [106]. Gut microorganisms secrete neurotransmitters, neuromodulators, and other amino acid-derived metabolites [107,108]. Indeed, both the microbes and the synthetics released have the potential to cause an inflammatory response or accelerate amyloid formation, leading to impaired memory and cognitive functioning. Therefore, maintaining a balance between intestinal microorganisms is important.

3.5.1. Gut microbial metabolites and inflammation

Several genetic changes in gut microbes are associated with CCAAT-enhancer-binding protein (C/EBPβ)/asparagine endopeptidase (AEP) signaling, which increases levels of pro-inflammatory enzymes associated with polyunsaturated fatty acid metabolism (Fig. 3) [12,109]. In addition, the activation of C/EBPβ signaling would further elevate AEP, resulting in increasing levels of APOE4, APP, Aβ, and tau [109], eventually inducing inflammation and cognitive impairment. The gut flora and the gut form a microbial gut axis that communicates bidirectionally through cytokines, hormones, and neural signals (Fig. 3) [110]. Furthermore, the diversity of gut microorganisms is strongly linked to the oral flora [111,112]. Periodontitis greatly increases the number and variety of oral pathogens, such as lipopolysaccharides (LPS), flagellins, peptides, as well as pro-inflammatory molecules. If these molecules overactivate systemic inflammatory responses, they may lead to neuroinflammation and AD [113].

3.5.2. Gut-microbe-brain axis

Intercommunication between the gut flora and brain was first introduced by William James and Carl Lange in the 1880s [114]. Evidence indicates that the microbiota continuously produces LPS and amyloids in healthy individuals. When these substances accumulate to a certain level in the body, they can be harmful, particularly when the permeability of the gut-blood-brain barrier undergoes significant changes in adult individuals [110,115]. When tight junctions between gut cells are compromised, permeation is enhanced and these tight junctions are unable to prevent LPS from entering the circulation, exacerbating the inflammatory response (Fig. 3) [116]. Intraperitoneal administration of LPS promotes the production of inflammatory factors and Aβ in the mice hippocampus. Additionally, mice develop cognitive dysfunction [117]. LPS activates microglia surface receptors through myeloid differentiation factor 88 and nuclear factor-kappa beta (NF-κB)-dependent signaling pathways, thereby promoting cytokine (Fig. 3) and chemokine production [118,119]. Extracellular LPS has also been reported to trigger microglial NOD-like receptor protein 3 inflammasome activation, increasing the level of ROS and IL-1β [120], which may be related to AD. In conclusion, the intestinal secretion of LPS induces an inflammatory response by binding to multiple neuronal cell receptors and promoting AD.

Gut microbes also produce bile acids (BAs) [121]. Increased bacterially produced BAs may increase BBB permeability and allow peripheral cholesterol to reach the CNS by disrupting tight junctions. This refers to the allowance of BAs, or cholesterol, from the periphery for entry into the CNS [122]. Cellular cholesterol in the brain can directly bind to APP, contributing to the insertion of APP into the lipid raft phospholipid monolayers that form Aβ and ultimately promoting Aβ production [123]. Microbial amyloid and Aβ42 are also recognized by the TLR2/TLR1 receptor, which activates the production of inflammatory factors. Microglia play an important role in preventing Aβ damage to neurons in healthy humans. Normally, activated microglia surround Aβ and prevent its diffusion, thus reducing the binding of Aβ to nearby neurons and mitigating neuronal damage [124]. Moreover, maintenance of intestinal microbial homeostasis is a prerequisite for the maturation and function of microglia, thereby protecting neurons from Aβ damage [125].

In summary, compounds produced and secreted by bacteria induce a systemic inflammatory response, increase BBB permeability,

and ultimately contribute to the development of neurodegenerative diseases, including AD [126,127].

3.6. miRNA dysregulation

miRNAs are usually dysregulated in the brains of patients with AD; they regulate neuronal growth, synapse formation, and plasticity.

3.6.1. miRNA dysregulation leads to Aβ deposition

Research has shown that miR-409-5p [128] and miR-30b [129] are upregulated in the brains of patients with AD. These miRNAs are thought to be involved in the process of AD by regulating Aβ formation. The overexpression of miR-409-5p had deleterious effects on neurite growth, reduced neuronal survival, and accelerated Aβ accumulation [128]. Song et al. provided the first evidence that miR-30b strongly upregulates ephrin type-B receptor 2 (ephB2), sirtuin1 (sirt1), and glutamate receptor subunit 2 (GluA2) to protect synapse integrity [129]. Their further research found that Aβ42 and cytokines promote miR-30b overexpression through NF-κB and then impair synaptic integrity by downregulating ephB2, sirt1, and GluA2, ultimately resulting in AD. In addition, Long J.M. et al. identified a novel miRNA region, miR-346, which up-regulates APP by targeting the 5′-untranslated region (UTR) of APP mRNA [130].

Additionally, miRNAs regulate Aβ levels by controlling the expression of BACE1 and APP. Wang et al. discovered that specific cortical regions implicated in AD pathology showed decreased neuronal miR-107 expression and increased BACE1 levels [131]. The 3′-UTR of BACE1 mRNA is targeted by miR-107, promoting the production of Aβ and contributing to the development of AD. In addition to BACE1, miRNAs can influence Aβ production by modulating α-secretase. α-Secretase ADAM10 inhibits Aβ formation, while miR-144 promotes AD progression by suppressing ADAM10 production through its 3′-UTR [132].

3.6.2. miRNA dysregulation leads to tau phosphorylation

Tau is a critical marker of AD and, several miRNAs regulate tau phosphorylation. In vivo, the expression of miR-125b contributes to tau phosphorylation, and Banzhaf-Strathmann found that miR-125b inhibits the expression of DUSP6, PPP1CA, and Bcl-W [133]. Downregulation of phosphatases and Bcl-W is accompanied by tau phosphorylation. Signals involved in tau phosphorylation, including p35, CDK5, and p44/42-MAPK, were upregulated [133]. Additionally, the deletion of miR-132 increases tau phosphorylation by activating ERK1/2 and BACE1 and upregulating inositol 1,4,5-trisphosphate 3-kinase B [134]. Downregulation of miR-34a

Table 1
miRNAs associated with AD.

NO.	miRNA	Function	Target gene	Expression in AD	Reference
1	miR-409-5p	Accelerated Aβ accumulation	Plek 3′UTR or Sdcbp2 3′UTR	↑ in AD	[128]
2	miR-30b	Affects synaptic integrity	3′UTR of ephB2, sirt1 or GluA2	↑ in AD	[129]
3	miR-346	accelerated APP formation	5′UTR of APP mRNA	↑ in AD	[130]
4	miR-107	Elevated BACE1 levels	3′UTR of the BACE1 mRNA	↓ in AD	[131]
5	miR-144	Accelerated Aβ accumulation by suppressing the production of ADAM10	3′UTR of ADAM10 mRNA	↑ in AD	[132]
6	miR-125b	Leads to tau phosphorylation and inducing neuro-inflammation by NF-κB	3′UTRs of DUSP6, PPP1CA, Bcl-W,15-LOX and mRNAs	↑ in AD	[133, 137]
7	miR-132	Leads to tau phosphorylation	3′UTR of ITPKB	↓in AD	[134]
8	miR-34a	Leads to tau phosphorylation	3′UTR of tau	↓ in AD	[135]
9	miR-106b	Leads to tau phosphorylation	3′UTR of CDK5	↓in AD	[133]
10	miR-743a	Suppress malate dehydrogenase activity to reduce ATP	3′UTR of mdh2	↓ in AD	[138]
11	miR-146a	switched the microglial phenotype, reduced pro-inflammatory cytokines, and en-hanced phagocytic function	3′UTR of Nkd2	↓ in AD	[139]
12	miR-331-3p	Accelerated Aβ accumulation	3′UTR of Sqstm1	↑ in AD	[140]
13	miR-9-5p	Accelerated Aβ accumulation	3′UTR of Optn	↑ in AD	[140]
14	miR-504-3p	Reduces tau phosphorylation	3′UTR of p39	↓ in AD	[141]
15	miR-124	Accelerated Aβ accumulation	3′UTR of PTPN1	↑ in AD	[142]
16	miR-22-3p	Reduced Aβ accumulation	Sox9	↓ in AD	[143]
17	miR-338	Decreases metabolic activity in axonal mitochondria	3′UTR of COXIV	↑ in AD	[144]
18	miR-98	reduced the production of Aβ and improved oxidative stress and mitochondrial dysfunction	3′UTR of HEY2	↓ in AD	[145]

Abbreviation: Ple, pleckstrin; Sdcbp2, syndecan Binding Protein 2; UTR, untranslated region; EphB2, ephrin type-B receptor 2; Sirt1, sirtuin1; GluA2, glutamate ionotropic receptor AMPA type subunit 2; APP, amyloid-β peptide precursor protein; BACE1, β-site APP cleaving enzyme 1; DUSP6, dual-specific phosphatase 6; PPP1CA, protein phosphatase 1 catalytic subunit alpha isoform; Bcl-W, Bcl-2-like protein 2; 15-LOX, 15-lipoxygenase; mRNAs, VDR messenger RNAs; ITPKB, inositol 1,4,5-trisphosphate 3-kinase B; CDK5, Cyclin-dependent Kinase 5; mdh2, mitochondrial tricarboxylic acid cycle gene; Sqstm1, Sequestosome 1; Optn, Optineurin; PTPN1, tyrosine-protein phosphatase non-receptor type 1; HEY2, split (Hes)-related with YRPW motif protein 2.

[135] and miR-106b [136] is also involved in tau phosphorylation, resulting in cognitive impairment.

In addition to Aβ and tau phosphorylation, miRNAs can also regulate various AD processes, such as mitochondrial function, enzyme, and microbial activities. The relevant information is presented in Table 1.

4. Drugs for the treatment of Alzheimer's disease

4.1. FDA-approved drugs in the past

Over the past 20 years, only five drugs have been approved by the FDA for the treatment of AD, the most common of which are AChE inhibitors, including tacrine, donepezil, rivastigmine, galantamine, and an N-methyl-D-aspartic acid (NMDA) receptor antagonist, memantine. Tacrine was the first clinically approved cholinesterase inhibitor but was withdrawn because of its high hepatotoxicity [146]. Donepezil demonstrated equal efficacy and a better safety profile than other AChE inhibitors [147]. Memantine was the first drug approved by the FDA to treat moderate-to-severe AD in 2003 [148,149]. These drugs have a significant limitation in that they can only alleviate symptoms without preventing or slowing disease progression, and both classes of drugs are associated with serious side effects. As a result, the current phase of drug development has shifted to targeting the pathogenesis of AD, with the largest number of drugs targeting Aβ and Tau for the treatment of AD. In recent years, AD drugs approved by the Food and Drug Administration (FDA) include aducanumab, lecanemab, and donanemab. The details are presented in Table 2.

4.2. FDA-approved drugs in recent years

4.2.1. Aducanumab

Aducanumab, a monoclonal antibody to the Aβ protein, was approved by the FDA in 2021 [150]. However, the aducanumab research process has not been completed. Aducanumab's two global Phase III clinical trials, code-named ENGAGE and EMERGE,

Table 2
FDA-approved drugs in AD.

No.	Name of the Drug	Mechanism of Action	Efficacy (Drug group vs. placebo group)	Side effects	Reference
1	THA	AchE inhibitors	Improving the patient's cognitive ability	high hepatotoxicity	[146]
2	Donepezil	AchE inhibitors	Improving the patient's cognitive ability	Gastrointestinal side effects	[151]
3	Revastigmine	AchE inhibitors	Improving the patient's cognitive ability	Gastrointestinal side effects	[152]
4	Galantamine	AchE inhibitors	Improving the patient's cognitive ability	Gastrointestinal side effects	[149]
5	Menantine	NMDA receptor antagonists	Improving the patient's cognitive ability	Dizziness, headache, confusion, diarrhea, and constipation	[149]
6	Aducanumab	monoclonal antibody to Aβ protein	1 .CDR-SB score decreased by 22 % in the drug group (P = 0.012); 2 . MMSE decreased by 18 % in the drug group (P = 0.049); 3 . ADAS-Cog 13 decreased by 27 % in the drug group (P = 0.010); 4 . ADCS-ADL-MCI decreased by 40 % in the drug group (P < 0.001).	ARIA-E, headache, ARIA-H, nasopharyngitis, falls, and dizziness	[153]
7	lecanemab	humanized IgG1 monoclonal antibody to Aβ protein	1 CDR-SB score decreased by 27 % in the drug group (P < 0.001); 2 ADAS-cog14 score decreased by 26 % in the drug group (P < 0.001); 3 ADCOMS decreased by 23 % in the drug group (P < 0.001); 4 ADCS-MCI-ADL score decreased by 36 % in the drug group (P < 0.001).	headache, infusion-related reactions, and ARIA, Lecanemab to be used with caution in patients with ApoEε4 homozygotes	[154]
8	donanemab	An antibody drug that targets N3pG (modified β amyloid plaques)	1 iADRS decreased by 22 % in the drug group (P < 0.0001); 2 CDR-SB score decreased by 29 % in the drug group (P < 0.0001); 3 Reduce the risk of progression to the next stage of the disease by 37 % (HR = 0.626; p < 0.0001).	Severe ARIAs may occur	[155]

Abbreviation: THA, Tacrine; AchE, acetylcholinesterase; NMDA, N-Methyl-D-aspartic acid; CDR-SB score, Clinical Dementia Rating–Sum of Boxes score; MMSE, Mini-Mental State Examination; ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale–13 items; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ARIA, amyloid-associated imaging abnormalities; ARIA-E, Amyloid-related imaging abnormalities due to edema/sulcal effusion; ARIA-H, Amyloid-related imaging abnormalities due to haemosiderin deposition; ADAS-cog14 score, 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCOMS, Alzheimer's Disease Composite Score; iADRS, integrated Alzheimer Disease Rating Scale.

showed different results. However, after analyzing a larger dataset, medical data statisticians found that aducanumab had a significant effect compared with the placebo. Clinical Dementia Rating-Sum of Boxes (CDR-SB) is the primary endpoint score, with higher scores indicating greater impairment. High-dose aducanumab (10 mg/kg target dose) reduced CDR-SB scores by 22 % at week 78 compared to the placebo group. Three other pre-specified secondary endpoints were as follows: an 18 % decrease in Minimum Mental State Examination, a 27 % decrease in Alzheimer's Disease Assessment Scale–Cognitive Subscale13, and a 40 % decrease in The Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment in the high-dose group relative to the placebo group. The details are presented in Table 2.

4.2.2. Lecanemab

Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, is being tested in patients with early AD, which reverses the pathological progression of AD and delays the clinical course of the disease by removing toxic Aβ proteins from the brain. This study [154] showed a 27 % slowing of cognitive and memory function decline in patients after 18 months of treatment with lecanemab compared to placebo. Lecanemab became the first Aβ-targeted drug in history to be fully approved by the FDA for AD treatment. The details are presented in Table 2.

4.2.3. Donanemab

Donanemab is an antibody drug that targets N3pG (modified β amyloid plaques), a subtype of amyloid [156]. Donanemab binds to and promotes the clearance of amyloid plaques. The results showed that donanemab significantly alleviated cognitive decline in patients with AD, with a more pronounced effect in patients with low-to-moderate tau levels. Patients with low-to-moderate tau levels had a 35 % decrease in the Integrated Alzheimer's Disease (AD) Rating Scale (iADRS) ($p < 0.0001$) and a 36 % decrease in CDR-SB scores ($p < 0.0001$) compared with 22 % and 29 % for all patients, respectively [155]. The details are presented in Table 2.

4.3. Common side effects of drugs

Amyloid-related imaging abnormalities (ARIA) are prevalent side effects of current Aβ antibody drugs, which can manifest as brain edema or sulcal effusion (ARIA-E) or as hemosiderin deposits in the brain parenchyma (ARIA-H microhemorrhage) or on the pial surface (ARIA-H superficial siderosis) [157]. The most common side effects of aducanumab are ARIA-E, headache, cerebral microhaemorrhage (ARIA-H microhaemorrhage), nasopharyngitis, falls, localized superficial scurfing (ARIA-H superficial scurfing), and dizziness [150]. In terms of safety, the incidence of cerebral edema and cerebral hemorrhage caused by lecanemab was relatively low compared to other comparable anti-Aβ drugs, at 12.6 % and 17.3 %, respectively [154]. In addition, a higher incidence of ARIA was found in patients who were homozygous for the ApoE ε4 allele after receiving lecanemab, and lecanemab should therefore be used with caution [154]. Of the patients treated with donanemab, 24 % developed ARIA-E and 31 % developed ARIA-H, most of which were mild to moderate. The details are presented in Table 2.

4.4. Future directions for drug development

Based on the existing FDA-approved drugs, most of the drugs are AChE inhibitors and Aβ amyloid-targeting drugs. Future investigations may focus on targeting the upstream molecules of Aβ, such as α-secretase, BACE1, BACE2, and γ-secretase to inhibit Aβ deposition, including lanabecestat and umibecestat. However, lanabecestat has been associated with adverse events during clinical trials [158], forcing the termination of the trials. Neuregulin 1 plays an important role in normal human psychiatric behaviors, and

Table 3
Selected AD drugs in clinical trial phase 3. The information comes from [160,161].

No.	Name of the Drug	Mechanism of Action	Clinical Trial
1	Gantenerumab	Anti-amyloid monoclonal antibody	NCT01760005
2	Remternetug	Anti-amyloid monoclonal antibody	NCT05463731
3	Solanezumab	Anti-amyloid monoclonal antibody	NCT01760005
4	Lanabecestat	BACE1 reversible inhibition	NCT0224573, NCT02783573
5	Umibecestat	BACE1 reversible inhibition	NCT03131453
6	Verubecestat	BACE1 reversible inhibition	NCT02910739
7	Elenbecestat	BACE1 reversible inhibition	NCT02956486
8	Atabecestat	BACE1 reversible inhibition	NCT03587376, NCT02569398
9	Semagacestat	γ-secretase inhibitor	NCT01035138
10	Tarenflurbil (MPC-7869)	γ-secretase inhibitor	NCT00322036
11	E2814	Anti-tau monoclonal antibody	NCT01760005, NCT05269394
12	Fosgonimeton	Activates signaling via the HGF/MET receptor system; promotes survival of neurons, enhances hippocampal synaptic plasticity.	NCT04488419, NCT04886063
13	Levetiracetam	Modulator of the SV2A to reduce aberrant neuronal hyperactivity	NCT05986721

Abbreviation: HGF, hepatocyte growth factor; SV2A, synaptic vesicle protein.

seizure protein 6 contributes to the maintenance of dendritic strength and prolonged sustained tension, both of which are substrates for BACE1; thus, the use of BACE1 inhibitors leads to adverse psychiatric events [158]. Although, BACE inhibitors have shown good performance in reducing Aβ deposition, they are inadequate in terms of safety. Other BACE inhibitors may also cause adverse reactions for similar reasons. Additional information is presented in Table 3. In addition, the pathogenesis of AD is complex and varied, including p-tau, neuroinflammation, ferroptosis, imbalance of the intestinal flora, miRNA dysregulation, and many other mechanisms. In future, we plan to develop more targeted and universal drugs based on these pathogenic mechanisms of AD. Additional information is presented in Table 3.

In addition to the pathogenesis of AD, some scientists are now proposing that neural stem cell (NSC) transplantation could emerge as a novel therapy for neurodegenerative diseases [159]. The primary objective of NSC replacement was to restore degenerating neurons, thereby delaying neuronal function and cognitive decline. Furthermore, recent reports suggest that NSCs also exhibit the ability to promote neurotrophin secretion [159]. The pathogenesis of AD is complex, and AD drugs cannot be studied in a single direction. The development of AD drugs should not only improve the cognitive dysfunction of patients with AD and slow down the disease process, but also, increase the safety of the drugs as much as possible. Therefore, based on an in-depth study of the different mechanisms, discovering the interactions between different mechanisms is very important for the development of new AD drugs.

5. Conclusion

AD involves various triggers, including family genetics, old age, and lifestyle habits. The prevalence of AD is increasing every year as the standard of living improves and the population ages significantly. In response to this global health problem, the drugs approved by the FDA are mainly divided into three categories, namely AChE inhibitors, NMDA receptor antagonists, and Aβ protein monoclonal antibodies [146,150]. To date, no drug can completely cure AD, which may be related to the complex and intertwined pathogenic mechanisms of AD. Consequently, many drugs that target pathogenic mechanisms, such as p-tau, neuroinflammation, mitochondrial oxidative stress, ferroptosis, the intestinal environment, and miRNA, are present [160]. Most drugs are terminated during clinical trials for a variety of reasons, with common reasons such as drug ineffectiveness and serious side effects. Therefore, the development of new therapeutics for AD remains challenging. However, owing to the complex pathological mechanisms of AD, a single target may have little effect. Perhaps we should consider a combination of drugs for multi-targeted therapy. For example, the combination of donepezil and memantine is associated with greater improvements in cognitive and daily activities and neuropsychiatric symptoms than monotherapy [162]. In the future, multi-target AD therapy may be a powerful means of treating AD.

CRediT authorship contribution statement

Liting Peng: Writing – original draft, Visualization. **Zhiming Zhang:** Writing – review & editing, Writing – original draft. **Qi Li:** Writing – review & editing, Visualization. **Zhenjiang Song:** Visualization. **Canqun Yan:** Writing – review & editing. **Hongyan Ling:** Writing – review & editing, Conceptualization.

Data availability

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Funding

This work was supported by the Natural Science Foundation of Hunan Province, China (No. 2021JJ30595, 2021JJ50096), and the Health Commission Foundation of Hunan Province, China (No. C202303076198, 202203064882).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We express our heartfelt gratitude to Language company (https://webshop.elsevier.com/language-editing-services/language-editing/), who gave us much help to improve the description.

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