Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.35425

Roles of Microglia and Astrocytes in Neuroinflammation of Alzheimer's Disease: From Mechanisms to Therapeutics

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Abstract. Alzheimer's disease (AD) is one of the most common types of neurodegenerative diseases. Its pathogenesis involves the interaction of multiple factors, including β-amyloid deposition, excessive tau protein phosphorylation, neuroinflammation, and synaptic dysfunction. Among these, neuroinflammation is widely recognized as a key factor driving the onset and progression of AD. As the two main types of glial cells in the central nervous system, microglia and astrocytes play central roles in the regulation of neuroinflammation. This paper systematically reviews the structural characteristics and functional states of microglia and astrocytes in AD-related neuroinflammation, as well as their interactions with Aβ and tau pathologies. Both types of glial cells exhibit a bidirectional transition from a protective to a damaging phenotype. In the early stage, they exert neuroprotective effects by phagocytosing and clearing abnormal proteins and releasing neurotrophic factors. Under sustained inflammatory stimulation, both gradually shift to a pro-inflammatory activated state, releasing large amounts of inflammatory factors, disrupting the blood-brain barrier and glymphatic system, and abnormally phagocytosing synaptic structures, forming a vicious cycle in which pathological protein deposition and excessive glial cell activation mutually exacerbate each other. More importantly, the two types of glial cells interact through various pathways such as cytokines, complement pathways, and signaling molecules, jointly amplifying the inflammatory cascade. This paper also summarizes therapeutic strategies for drugs targeting these two glial cells, including cholinesterase inhibitors, NMDA receptor antagonists, non-steroidal anti-inflammatory drugs, and biological agents targeting Aβ and tau proteins. In conclusion, functional abnormalities and interactive disorders of microglia and astrocytes are the core driving factors of AD neuroinflammation. An in-depth understanding of the molecular mechanisms underlying their interaction will provide a new breakthrough for shifting AD treatment from symptomatic management to etiological eradication.

Keywords: Alzheimer's disease, microglia, astrocyte, neuroinflammation, interaction, therapeutic strategy

1. Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases worldwide and a major cause of dementia. Statistics show that 60% to 80% of all dementia cases are caused by AD

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DOI: 10.54254/2753-8818/2026.35425

[1]. In patients with AD, neurons in brain regions responsible for memory, language, and thinking, such as the hippocampus, are first damaged and destroyed, so patients' memory, language, and cognition are affected first [2].

The pathogenesis of AD involves the joint participation of multiple factors, including β-amyloid (Aβ) deposition, abnormal tau protein phosphorylation, neuroinflammation, synaptic dysfunction, and brain-gut axis dysfunction, all of which are interrelated and act as inducing factors for each other [3]. Among them, neuroinflammation is considered one of the key pathogenic factors in the occurrence and development of AD [4]. Microglia and astrocytes are significantly activated in the neuroinflammatory microenvironment. They act synergistically with various inflammatory cytokines and chemokines to damage neurons and their survival microenvironment, exacerbate oxidative stress, induce apoptosis, and promote the progression of AD. Numerous studies have shown that these two types of glial cells not only participate in the pathological processes of Aβ and tau proteins respectively, but also have complex interactions that jointly drive the occurrence and evolution of neuroinflammation. Abnormal expression of Aβ and tau proteins can damage the normal tissue structure of the patient's brain, induce neuroinflammation, and play an important role in the progression of AD at all stages. Under pathological conditions, Aβ aggregates extracellularly to form amyloid deposits, and hyperphosphorylated tau protein forms neurofibrillary tangles (NFTs) inside neurons and glial cells. These abnormal processes activate microglia, promote their proliferation, and lead to neuroinflammation [5]. Autopsy studies have shown that activated microglia are significantly increased in the hippocampus of AD patients and aggregate in and around the core of Aβ plaques [6].

Aβ is formed by proteolytic cleavage of amyloid precursor protein (APP), among which Aβ42 is a key type that promotes the formation of amyloid plaques and causes AD pathogenesis [7]. Mutations in genes such as the human APP gene can increase Aβ production, raise the Aβ42/Aβ40 ratio, and promote plaque formation [8]. Pyroglutamyl-containing Aβ peptides are more likely to form β-sheet structures than full-length Aβ peptides, and are more stable and prone to aggregation, with significantly higher levels in the brains of AD patients [9, 10]. Jamasbi et al. found that phosphorylated Aβ42 forms more β-sheets in a lipid synthesis environment and can rapidly form aggregates [9]. Aβ monomers easily aggregate to form soluble oligomers, protofibrils, and insoluble amyloid fibrils. Pharmacological evidence shows that the severity of cognitive dysfunction in AD patients is more correlated with soluble Aβ levels than with insoluble Aβ [11]. Therefore, abnormal metabolism and aggregation of Aβ, especially the formation of soluble oligomers, are the key molecular basis of AD pathogenesis.

Tau protein is one of the microtubule-associated proteins, involved in axonal transport and growth, and neuronal polarization [12]. Tau protein is derived from the *MAPT* gene and produces six isoforms through alternative splicing, with differential expression in different cell types and tissues [13]. Due to carrying excess positively charged residues, tau protein lacks a fixed three-dimensional structure, is highly flexible, and is prone to misfolding [14]. Tau protein is phosphorylated by kinases such as CDK-5 and GSK-3β, and phosphorylation at sites such as Thr231 and Ser262 affects its affinity for microtubules. Hyperphosphorylation increases its tendency to self-aggregate. Studies on human AD brain tissue have found that synapse-associated proteins can interact with phosphorylated tau protein [15], causing it to mislocalize to dendritic spines and impair synaptic function. Most of the acetylation and ubiquitination sites of tau protein overlap, and acetylation blocks ubiquitination-mediated clearance, slowing degradation and leading to pathological tau accumulation. Some studies have also pointed out that acetylation of the KIGS motif can inhibit tau aggregation in AD brains, indicating that acetylation at different sites has different effects on its

DOI: 10.54254/2753-8818/2026.35425

pathogenicity. *MAPT* gene mutations, abnormal post-translational modifications, combined with cellular stresses such as oxidative stress and inflammation, jointly lead to tau protein misfolding. Specific motifs in the MTBD region form β-sheets, driving tau monomers to aggregate into soluble oligomers, which then spread to multiple brain regions through a prion-like mechanism, forming insoluble NFTs, disrupting cellular function and inducing adjacent neurons to form new NFTs [16].

Although the academic community has conducted extensive research on the role of neuroinflammation in AD and the independent functions of microglia and astrocytes, there is still a relative lack of systematic discussion on how the two work together to drive neuroinflammation. Therefore, this paper aims to systematically elaborate the core roles of microglia and astrocytes and their mutual regulatory mechanisms in AD neuroinflammation, and discuss the development prospects of related therapeutic strategies targeting these two glial cells.

2. Microglia and neuroinflammation in AD patients

2.1. Structure and function of microglia

Microglia originate from erythromyeloid precursors in the yolk sac and migrate to the central nervous system for differentiation and maturation in early embryonic development. Mature microglia can take on various morphologies: ramified microglia are responsible for monitoring abnormalities, while amoeboid microglia have strong phagocytic and migratory abilities and are responsible for clearing pathogens and cell debris. It remains unclear whether specific functions are associated with specific morphologies [17].

During the embryonic and early postnatal periods, microglia lack characteristic branched processes and differ greatly in function from those in adulthood. Studies in rats and primates have found that microglia can control the number of cortical neurons by phagocytosing neural precursor cells. Depletion of microglia in the uterus during pregnancy significantly increases hypothalamic cell death and leads to the accumulation of dead cells. Meanwhile, microglia stimulate neurogenesis by supporting the survival, proliferation, and maturation of neural precursor cells and neurons. Experiments have shown that insufficient insulin-like growth factor 1, a neurotrophic factor produced by embryonic microglia, fails to support the survival of early postnatal neurons [18]. In adulthood, microglia can efficiently phagocytose synaptic material. Rachel et al. found that long-term elimination of microglia in the brains of adult mice after neuronal injury increases dendritic spine density [19]. In addition, blocking the secretion of brain-derived neurotrophic factor by microglia leads to reduced formation of cortical dendritic spines, accompanied by learning deficits, indicating that microglia are not only involved in synaptic elimination but also in synaptogenesis [20].

2.2. Microglia and neuroinflammation

Neuroinflammation is a sustained inflammatory response in the central nervous system involving multiple immune and non-immune cells. Early acute neuroinflammation can defend against pathogens and clear cell debris, but persistent inflammation evolves into a chronic pro-inflammatory response that exacerbates neuronal damage [5]. In response to neuroinflammatory stimuli, microglia play a dual role. Microglia can be divided into resting (M0) and activated (M1 and M2) types. In the early stage of neuroinflammation, when brain homeostasis is impaired, damaged neurons release anti-inflammatory factors that promote their transformation into the M2 anti-inflammatory phenotype [8], releasing transforming growth factor-β, IL-4, IL-13, etc., to enhance phagocytosis.

DOI: 10.54254/2753-8818/2026.35425

However, sustained stimulation with LPS, TNF-α, or IFN-γ induces microglia to transform into the M1 pro-inflammatory phenotype that releases large amounts of pro-inflammatory factors such as TNF-α and IL-6, accompanied by impaired phagocytic function [21, 22].

Recent studies have found that under pathological conditions such as neurodegeneration or physical injury, microglial activation is a dynamic process rather than a simple binary classification of M1/M2. Meanwhile, the activation state of microglia can change with specific environmental conditions and is not strictly divided according to the stage of neuroinflammation. For example, microglia exposed to IFN-γ or LPS also upregulate pro-inflammatory genes such as IL-1β and TNF-α and release reactive oxygen species during acute neuroinflammation, exacerbating neuronal damage. In the tissue repair phase, microglia stimulated by IL-4 or IL-13 highly express homeostasis regulatory genes, promoting synaptic remodeling and remyelination [23].

2.3. Interactions between microglia and Aβ/tau proteins

Pathological deposition of Aβ and abnormal phosphorylation of tau protein in the brains of AD patients induce neuroinflammation, and a large number of microglia aggregate around Aβ plaques [24]. Successfully activated microglia can clear Aβ and tau proteins. TREM2 is a specific receptor on the surface of microglia that promotes M2-type transformation and phagocytic activity. Mouse experiments have shown that activating TREM2 can inhibit hippocampal neuroinflammation. TREM2 can interact with oligomeric Aβ and promote its endocytosis. Depletion of most microglia or TREM2 leads to an increase in phosphorylated tau protein and significantly enhanced spreading ability in mouse brains [25]. TREM2 can also bind heparan sulfate, promote the uptake of apolipoprotein E3 by microglia, and reduce extracellular toxicity. Meanwhile, long-term neuroinflammation leads to a gradual decrease in TREM2 expression and reduced anti-inflammatory effects [26]. However, these two pathological proteins can also inhibit the normal function of microglia. After treating microglia in mouse brains with various types of Aβ, including monomers and oligomers, all types of Aβ altered cell morphology and significantly increased the expression of pro-inflammatory factors [27]. TREM2 deficiency promotes the transregional spread of tau protein from the medial entorhinal cortex to the dentate gyrus of the hippocampus, exacerbating tau diffusion [28]. This indicates that although microglia can clear Aβ and tau, the long-term presence of pathological proteins triggers chronic neuroinflammation, gradually depleting TREM2 and reducing protein clearance, forming a vicious cycle.

2.4. Microglia-mediated neuroinflammatory pathways and AD

Multiple molecular pathways can affect microglial activation. TRPM2 is a calcium channel sensitive to oxidative stress. Aβ oligomers can activate microglia through TRPM2, and inhibiting TRPM2 expression can reverse Aβ-induced synaptic dysfunction and memory impairment [29]. Studies have shown that PQBP1 binds to tau protein and participates in the cGAS-STING pathway; depletion of PQBP1 can block tau-induced NF-κB activation and cognitive impairment [30]. Blocking NLRP3 can reduce tau phosphorylation levels and prevent its aggregation by affecting the activities of tau protein kinases and phosphatases, alleviating memory loss and reducing Aβ deposition [31, 32]. CX3CR1 is expressed on microglia; deletion of CX3CR1 reduces Aβ deposition but increases tau phosphorylation, while agonizing CX3CR1 ligand activity can reduce tau phosphorylation, neuronal death, and brain atrophy [33, 34].

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3. Astrocytes and neuroinflammation in AD patients

3.1. Structure and function of astrocytes

As the most abundant cell type in the mammalian brain, accounting for approximately 20% to 40%, astrocytes are divided into protoplasmic and fibrous types. They are widely connected to capillaries through end-feet, participating in blood-brain barrier maintenance, cerebral blood flow regulation, and metabolic support. The entire central nervous system is continuously and non-overlappingly covered by astrocytes [35], with sparser distribution in regions with high neuron density and richer distribution in regions with abundant dendrites and axons [36]. Although astrocytes do not generate action potentials, they can achieve excitability through Ca^{2+} signaling. In in vitro culture experiments, few synapses are formed and they are functionally immature in the absence of astrocytes; after adding astrocytes, the number of mature synapses increases sevenfold [37]. A single cortical protoplasmic astrocyte domain may contain 4 to 8 neuronal somas and 300 to 600 dendrites [38]. Astrocytes also maintain ion homeostasis through the AQP4 water channel, clear glutamate, and produce lactate through glycolysis to meet neuronal energy demands.

3.2. Astrocytes and neuroinflammation

Astrocytes are in a resting state under normal physiological conditions. When the environment changes or nerve injury occurs, they transform into reactive astrocytes, which are activated into different subtypes according to the degree of disease progression and perform different functions. In the early stage of injury, astrocytes are activated and mainly polarize into the anti-inflammatory A2 phenotype. This phenotype has neuroprotective effects and releases anti-inflammatory cytokines during AD. If neuroinflammation persists, A2 astrocytes will gradually polarize into the A1 phenotype, releasing pro-inflammatory cytokines and exacerbating neuroinflammation in the brain.

The progression of neuroinflammation is driven by reactive astrocytes through multiple pathways. First, reactive astrocytes express Toll-like receptors or other pattern recognition receptors on their surface, which can recognize damage-associated molecular patterns or pathogen-associated molecular patterns and generate responses, further activating downstream immune signaling pathways, such as nuclear factor κB family, activator protein-1 family, or interferon regulatory factor family transcription factor pathways. These pathways work together to induce the expression of inflammatory cytokines such as TNF-α, IL-1β, IL-6, and chemokines [39]. Astrocytes also express glutamate transporter 1 and glutamate-aspartate transporter 1 on their surface for clearing glutamate from the synaptic cleft. Studies have found that after astrocyte activation, the expression of these two transporters decreases, causing glutamate clearance dysfunction and elevated glutamate concentration in the synaptic cleft, which in turn leads to neuronal death through excitotoxicity. Moreover, neuroinflammation is often accompanied by abnormal lipid metabolism. Lipid metabolism in the brain mainly depends on astrocytes. When fatty acid load exceeds the oxidative phosphorylation capacity of astrocytes, corresponding mitochondrial dysfunction occurs and promotes the activation of signal transducer and activator of transcription, increasing astrocyte reactivity and accelerating the expression of pro-inflammatory factors [40]. Under inflammatory conditions, pro-inflammatory cytokines regulate astrocyte metabolic remodeling, promote the production of lactosylceramide, and activate downstream pathways, thereby activating the NF-κB-driven pro-inflammatory response pathway. This pathway also promotes the production of neurotoxic nitric oxide, aggravating nervous system damage [41]. Activated astrocytes secrete

DOI: 10.54254/2753-8818/2026.35425

related proteins under pathological conditions, affecting cerebrovascular endothelial integrity and exacerbating neuroinflammation.

An experiment treating mouse brains with a high-salt environment found that a high-salt environment promotes astrocytes to activate the NFκB/MMP-9 signaling pathway, leading to a significant increase in vascular endothelial growth factor (VEGF) expression. VEGF then induces the destruction of tight junctions in vascular endothelial cells by inducing phosphorylation and activation of downstream enzymes, exacerbating neuroinflammation [42]. Another study using a human induced pluripotent stem cell-derived blood-brain barrier co-culture model found that TNF can induce astrocytes to transform into an inflammatory reactive state, activate the signal transducer and activator of transcription 3 (STAT3) signaling pathway, promote downstream α1-antichymotrypsin expression, and destroy vascular endothelial tight junctions. Meanwhile, specific silencing of the α1-antichymotrypsin gene in mouse astrocytes can reduce TNF-induced vascular inflammation and alleviate neuroinflammation [43].

3.3. Interactions between astrocytes and Aβ/tau proteins

Aβ and tau proteins activate astrocytes to polarize into a reactive phenotype. Autopsy and animal models show reactive astrocytes near Aβ plaques [44]. They have neuroprotective effects, can form glial scars to surround Aβ plaques, and reduce Aβ deposition through phagocytosis.

GFAP is derived from reactive astrocytes and can be used as a blood biomarker for early AD screening [45]. Knockout of the *GFAP* gene leads to reduced hypertrophic processes of astrocytes and decreased contact with plaques; even when Aβ load is restored, GFAP deficiency still leads to a significant increase in dystrophic neurites, indicating that astrocyte activation can limit plaque growth [46]. Astrocytes metabolize tau through the autophagy-lysosome pathway, and activating TFEB can enhance the activity of this pathway. Activating PPARA-mediated autophagy and lysosome pathways can reduce Aβ deposition and improve cognition [47]. APOE3-Ch astrocytes exhibit abnormal lipid homeostasis and decreased ceramide levels, endocytose tau oligomers more efficiently than wild-type cells, degrade them through lysosomal and proteasomal pathways, and show reduced tau secretion [48].

As pathology persists, astrocytes will transform into a pro-inflammatory state. Overexpression of S100β increases Aβ42 levels, and inhibiting S100β can reduce gliosis and Aβ deposition [45]. APOE4 is the strongest genetic risk factor for late-onset AD [5]. Astrocytes carrying APOE4 show reduced response to Aβ stimulation and cannot support themselves and microglia in phagocytosing Aβ [49]. Aβ can induce increased expression of BACE1 and APP in astrocytes, producing more Aβ and increasing BACE1 activity, forming a positive feedback loop [44, 50]. The brain environment of AD patients causes endoplasmic reticulum stress in astrocytes, activates the PERK-eIF2α pathway, causes abnormal AQP4 localization, and impairs glymphatic clearance function; inhibiting PERK signaling can restore AQP4 localization, reduce Aβ and tau deposition, and improve cognition [51]. Specific deletion of the *BMAL1* gene in astrocytes significantly promotes BAG3 expression and enhances the ability to phagocytose and degrade extracellular tau [52].

4. Interactions between microglia and astrocytes in AD

When central nervous system homeostasis is disrupted, microglia and astrocytes are activated: microglia polarize into activated types and astrocytes polarize into reactive types. According to their different functions, both are divided into pro-inflammatory and anti-inflammatory phenotypes. The interaction between the two types of cells plays a key role in the regulation of neuroinflammation.

DOI: 10.54254/2753-8818/2026.35425

Both microglia and astrocytes can secrete a variety of cytokines, which can further stimulate each other and promote the secretion of inflammatory factors. In vitro studies have found that culturing astrocytes with the culture medium of mouse microglia treated with LPS significantly increases the expression of GFAP, IL-1β, and TNF-α in astrocytes. Meanwhile, adding 0.5% to 1% microglia to high-concentration astrocytes stimulated by LPS also significantly increases the expression of TNF-α and inducible nitric oxide synthase, indicating that both types of cells can promote the production of inflammatory molecules by the other [53]. In addition to producing pro-inflammatory factors, these cytokines can also regulate the functions of both parties. IL-33 is derived from astrocytes, and researchers found in studies of mouse brains that microglial synaptic remodeling is affected by IL-33 [54]. A high-salt diet causes microglia to prune astrocytic processes. When culturing rats, researchers found that high salt activates microglia, causing them to aggregate around vasopressinergic neurons in the supraoptic nucleus and paraventricular nucleus, and prune astrocytic processes near vasopressinergic neurons, inhibiting their metabolism of glutamate in the synaptic cleft. Elevated glutamate can activate extrasynaptic N-methyl-D-aspartate receptors, promoting tonic activation of vasopressinergic neurons to release large amounts of vasopressin and regulate blood pressure [55].

Endocannabinoids are naturally occurring signaling molecules in the human body with effects similar to cannabis. They can activate microglia in the amygdala during the perinatal period, enhance their phagocytic activity, and phagocytose newborn astrocyte precursors, leading to a decrease in their number, which reduces glutamate clearance in the synaptic cleft and increases neuronal excitability [56]. Microglia have IL-3 receptors on their surface, which can bind to IL-3 and regulate cell function. Under resting conditions, astrocytes continuously and stably express IL-3, but since microglia express a small amount of IL-3 on their surface, they cannot produce corresponding responses. After neuroinflammation occurs, microglia undergo an activation reaction, increasing the expression of IL-3 receptors on their surface, allowing the two to bind and regulate their transcription, morphology, and function [57]. Microglia can also regulate astrocytes by releasing signaling molecules. An experiment inducing synaptic clearance in the barrel cortex of newborn mice showed that before microglia perform phagocytosis, they release Wnt signaling molecules to induce and activate the corresponding Wnt receptor pathway in astrocytes, promoting astrocytic process remodeling and causing them to retract from around synapses, creating space for microglia to phagocytose synapses [58]. After central nervous system injury, a special subset of astrocytes aggregates at the injury boundary. Stimulated by type I interferon, these cells specifically and highly express bone marrow stromal antigen 2 (BST2). BST2 directly binds to and activates PKCβII and initiates the NF-κB signaling pathway, promoting the transcription and secretion of complement C3, which further binds to C3 receptors on the surface of microglia and activates microglia to aggregate in large numbers at the injury boundary, aggravating nerve damage. After knocking out the astrocyte-specific *BST2* gene in mice, researchers found that the interaction between the two types of glial cells in the brain was weakened, boundary formation was reduced, and early nervous system injury could be improved [59].

5. Drug therapies for AD targeting microglia and astrocytes

5.1. Cholinesterase inhibitors

Cholinesterase inhibitors (ChEIs) are among the earliest drugs used for AD treatment. Early studies found that in AD patients, the basal nucleus of Meynert in the basal forebrain undergoes severe neurodegeneration, with massive death of cholinergic neurons, severe depletion of presynaptic

DOI: 10.54254/2753-8818/2026.35425

cholinergic transmitters in the cerebral cortex, and significantly decreased choline acetyltransferase activity. Patients show reduced discrimination ability and memory impairment, while administration of cholinergic agonists to mice with the same symptoms alleviates the symptoms [60-64]. ChEIs can bind to cholinesterase and inhibit its function, slowing the metabolism of acetylcholine in the synaptic cleft and improving cholinergic system function. Studies have shown that ChEI use for 1 to 5 years in AD can slow the rate of cognitive decline, with slower degradation of cognitive and overall function in the patient group than in the placebo group [65].

The first-generation ChEI is tacrine, which has been basically discontinued due to its hepatotoxicity. The second generation includes donepezil, rivastigmine, and galantamine, which can effectively restore cognitive ability and overall mental status in patients with mild to moderate AD. ChEI drugs have few adverse reactions in most patients and high safety. Some patients experience dizziness and gastrointestinal adverse reactions such as diarrhea, nausea, vomiting, and decreased appetite. Among the main adverse reactions of the three drugs, diarrhea is most common with donepezil, vomiting with rivastigmine, and decreased appetite with galantamine; very few patients experience dizziness after taking ChEI drugs.

5.2. Excitatory amino acid receptor antagonists

Excitatory amino acid receptor antagonists used for AD treatment generally refer to non-competitive NMDA receptor antagonists. They can prevent glutamate from binding to NMDA receptors, avoid excessive leaked glutamate in the synaptic cleft from continuously activating receptors, inhibit abnormal sustained calcium influx, and thereby block the downstream excitotoxicity cascade, protecting neurons from damage.

The main drug of non-competitive NMDA receptor antagonists is memantine, which is the first drug approved by the FDA for the treatment of moderate to severe AD. It has the characteristics of moderate to low affinity and non-competitive voltage dependence, only blocking excessively open NMDA receptors without affecting NMDA receptors under physiological conditions, with no obvious side effects, and the frequency of adverse reactions is comparable to that of placebo [66]. Data from a cohort study showed that memantine can reduce the progression rate of AD and effectively delay the decline of cognitive function in patients [67]. In terms of combination therapy, adding memantine to donepezil monotherapy may be beneficial for patients with intermediate-stage AD or those with worsening cognitive status [68]. Multiple cohort studies have found that the combination of memantine and antipsychotics can significantly reduce the dosage of the latter, with a more significant reduction effect than ChEIs. Memantine is suitable for AD patients of different severity and is generally well tolerated, with rare adverse reactions such as nausea, dizziness, diarrhea, and agitation. When used clinically for moderate to severe AD, the safety of memantine combined with ChEI is comparable to that of ChEI monotherapy, with no additional risk of adverse reactions [65].

5.3. Non-steroidal anti-inflammatory drugs

Pathological protein deposition in the brains of AD patients leads to excessive activation of microglia and astrocytes, continuously promoting the occurrence of chronic neuroinflammation. Prostaglandins catalyzed by cyclooxygenase are important inflammatory factors related to inflammation in the body. Theoretically, non-steroidal anti-inflammatory drugs (NSAIDs) can block this pathological process by inhibiting the enzyme and reducing prostaglandin synthesis. An epidemiological study found that patients who took NSAIDs continuously for more than two years

DOI: 10.54254/2753-8818/2026.35425

had a significantly lower incidence of AD [64]. Animal model experiments have also proven that NSAIDs can act on microglia, promoting them to wrap Aβ plaques and form a microglial barrier around them to reduce plaque load [69]. However, more studies have found that the benefits of NSAIDs for AD remain to be confirmed. A meta-analysis showed that taking NSAIDs has no significant benefit on cognitive decline in patients, with no significant improvement in spatial orientation, concentration, etc. [70]. A large randomized trial including individuals over 70 years old with at least one family history of AD found that the treatment groups using naproxen and celecoxib among NSAIDs had an increased risk of AD instead, and the trial was terminated early due to increased heart disease risk in the naproxen group [69].

The current mainstream view is that NSAIDs should not be used for the treatment of patients with confirmed AD. However, since long-term chronic inflammation increases vascular permeability of the blood-brain barrier, peripheral inflammatory factors may enter the brain and aggravate neuroinflammation, the peripheral anti-inflammatory effect of NSAIDs is particularly important, providing new ideas for the treatment of AD.

5.4. Aβ-targeted drugs

Abnormal deposition of Aβ is a key initiating factor in AD pathogenesis. According to the classic amyloid cascade hypothesis, excessive production, aggregation, and deposition of Aβ can trigger a series of cascade reactions such as neuroinflammation and synaptic damage, ultimately leading to progressive cognitive decline. Therefore, drugs targeting Aβ itself are particularly important for the treatment of AD. This paper mainly introduces drugs that clear Aβ from the brain.

Drugs for clearing brain Aβ mainly include passive and active immunotherapies. Passive immunotherapy drugs achieve the purpose of clearing Aβ by injecting human-derived Aβ antibodies. Currently, the main drugs include aducanumab, lecanemab, and donanemab. Aducanumab was the first approved AD drug since 2003, and it can specifically target Aβ aggregates, including insoluble fibrils and soluble oligomers [70]. In a double-blind, placebo-controlled phase Ib clinical trial, monthly infusion of aducanumab for 12 consecutive months showed that the longer the infusion time and the higher the dose, the better the effect of reducing Aβ plaque load in the brain. Subsequent use found that patients experienced headache, dizziness, confusion, even cerebral edema, sulcal effusion, and cerebral microhemorrhage, causing huge controversy and criticism and leading to its withdrawal from the market [71, 72]. Lecanemab is a humanized IgG1 monoclonal antibody that readily binds to soluble Aβ protofibrils. After administering mouse-derived lecanemab to AD mice, it was found that Aβ protofibrils in their brains decreased and cognitive deficits in mice improved [71]. An 18-month, multicenter, double-blind phase 3 clinical trial found that lecanemab reduced Aβ levels in early AD, and in the cerebrospinal fluid subgroup study and plasma analysis of the overall population, lecanemab was superior to the placebo group in reducing Aβ protein, tau protein, neurodegeneration, and neuroinflammation markers [73]. A study on the safety of lecanemab found no deaths related to lecanemab during the core experimental period. Common adverse events included infusion-related reactions (24.5%), hemosiderin deposition-type amyloid-related imaging abnormalities (microhemorrhage, 16.0%), edema-type amyloid-related imaging abnormalities (13.6%), and headache (10.3%) [74], with overall good tolerance. Donanemab specifically binds to insoluble modified N-terminal truncated Aβ protein in amyloid plaques. A 76-week, randomized, double-blind, multicenter phase 3 clinical trial found that the donanemab treatment group achieved clinically meaningful benefits in both the iADRS and CDR-SB AD cognitive scales. Amyloid-related imaging abnormalities are the most common adverse reaction in patients, most of which are asymptomatic. If symptoms occur, they are mostly mild manifestations

DOI: 10.54254/2753-8818/2026.35425

such as headache and increased confusion; severe symptoms including epilepsy and even life-threatening conditions may also occur [75]. A meta-analysis including three monoclonal antibodies found that both donanemab and lecanemab were significantly superior to placebo in both cognitive indicators, while aducanumab was only superior to placebo in one cognitive indicator, suggesting that aducanumab has relatively weak efficacy in delaying cognitive impairment [76].

5.5. Tau-targeted drugs

In AD patients, abnormally phosphorylated tau protein continuously accumulates in the soma of neurons and glial cells and forms characteristic neurofibrillary tangles, affecting normal cell function. Drug targets related to tau protein are also one of the research ideas. Currently, only a few tau-targeted drugs have entered clinical trials, and most drugs are still in preclinical research [77], with drug ideas mainly limited to inhibiting tau protein phosphorylation, as shown in Table 1.

GSK-3β acts as a key enzyme catalyzing the phosphorylation of tau protein. Its abnormal activity can lead to abnormal tau protein phosphorylation, weakened microtubule stability, promotion of NFT formation, and increased Aβ production. Small-molecule GSK-3β inhibitors such as lithium, tideglusib, and valproic acid have been used in preclinical models, which can reduce GSK-3β activity, decrease tau phosphorylation and Aβ production. Natural compounds can also indirectly reduce GSK-3β activity. Curcumin and resveratrol can reduce GSK-3β activity through the PI3K/Akt pathway and exert neuroprotective effects by reducing oxidative stress and inflammation [78]. In terms of adverse reactions, GSK-3β can affect a wide range of metabolism, autophagy, DNA repair, and apoptosis, so global inhibition caused by drugs may produce off-target effects.

Table 1. Classification, mechanisms, efficacy, and adverse reactions of AD therapeutic drugs

Drug Category	Representative Drugs	Core Mechanism of Action	Clinical Efficacy	Main Adverse Reactions
Cholinesterase inhibitors	Donepezil, rivastigmine, galantamine	Inhibit cholinesterase, increase cholinergic transmitter levels in the synaptic cleft, and restore cholinergic system function	Improve cognition and daily ability in patients with mild to moderate AD, and slow the rate of cognitive decline	Diarrhea, nausea, vomiting, decreased appetite, dizziness; donepezil tends to cause diarrhea, rivastigmine tends to cause vomiting, galantamine tends to cause decreased appetite
Excitatory amino acid receptor antagonists	Memantine	Non-competitively block pathologically activated NMDA receptors, inhibit calcium influx, and antagonize excitotoxicity	Delay disease progression in moderate to severe AD, reduce the dosage of antipsychotics, and have better effects when combined with cholinesterase inhibitors	Nausea, dizziness, diarrhea, agitation, with low incidence
Non-steroidal anti-inflammatory drugs	Naproxen, celecoxib	Inhibit cyclooxygenase, reduce prostaglandin synthesis, and exert anti-inflammatory effects	Epidemiological data suggest that long-term use may reduce AD risk, but clinical improvement of cognition has not been confirmed; some studies show increased AD and heart disease risks	Gastrointestinal reactions, cardiovascular risks

DOI: 10.54254/2753-8818/2026.35425

Table 1. (continued)

Aβ-targeted antibody drugs	Aducanumab	Target Aβ aggregates and clear Aβ plaques in the brain	Can reduce Aβ plaque load, but cognitive benefit is limited	Headache, dizziness, cerebral edema, cerebral microhemorrhage, sulcal effusion
	Lecanemab	Bind soluble Aβ protofibrils and reduce Aβ levels	Significantly improve cognition in early AD, and reduce markers of neuroinflammation and tau	Infusion-related reactions, amyloid-related imaging abnormalities, headache
	Donanemab	Bind modified N-terminal truncated Aβ and clear amyloid plaques	Improve cognitive scores in early AD	Amyloid-related imaging abnormalities, mostly asymptomatic, occasional epilepsy
Tau-targeted drugs	Lithium, tideglusib, valproic acid	Inhibit GSK-3β activity and downregulate abnormal tau protein phosphorylation	Effective in preclinical models, a few have entered clinical trials	Produce off-target effects
	Curcumin, resveratrol	Indirectly inhibit GSK-3β through the PI3K/Akt pathway, with anti-inflammatory and antioxidant effects	Show neuroprotective effects in preclinical studies	

6. Summary and outlook

This paper systematically reviews the roles of Aβ pathological deposition, excessive tau protein phosphorylation, and neuroinflammation in the occurrence and development of AD, as well as the dual roles of microglia and astrocytes. AD is not simply neuronal degeneration, but a chronic neuroinflammation based on pathological protein deposition and driven by functional imbalance and interactive disorders of the two types of glial cells. In the process of AD neuroinflammation, both types of glial cells exhibit a bidirectional characteristic of transition from protective to damaging phenotypes: in the early stage, they protect nerves by phagocytosing abnormal proteins and releasing neurotrophic factors. Under sustained inflammatory stimulation, both gradually shift to pro-inflammatory activation, release a large number of inflammatory factors, destroy the blood-brain barrier and glymphatic system, and abnormally phagocytose synaptic structures, forming a vicious cycle in which pathological protein deposition and excessive glial cell activation mutually exacerbate each other, ultimately leading to progressive cognitive decline. Meanwhile, the two types of glial cells interact through cytokines, complement pathways, signaling molecules, and other pathways, jointly amplifying the inflammatory cascade. Existing treatments show that traditional ChEIs and NMDA receptor antagonists only play a symptomatic therapeutic role. Strategies aimed at inhibiting abnormal neuroinflammation and restoring glial cell function, such as drugs targeting Aβ and tau proteins, can interrupt the pathological vicious cycle from the source. In conclusion, functional abnormalities and interactive disorders of microglia and astrocytes are the core driving factors of AD neuroinflammation. Targeting these two types of glial cells is a key breakthrough for AD to break through the limitations of symptomatic treatment and achieve etiological treatment.

DOI: 10.54254/2753-8818/2026.35425

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