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# The role of astrocytes in Alzheimer's disease, A systematic review

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## Abstract

**Introduction:** Alzheimer's disease (AD), the most common neurodegenerative disease in the world, appears in two forms, early and late. Pathologically, an amyloid beta peptide is the hallmark of this disease which is followed by synaptic dysfunction, brain atrophy, and accumulation of neuronal tangles. The purpose of this study is to review the researchers on astrocytes' role in the progress of AD.

**Materials and Methods:** A comprehensive search was conducted in databases articles focusing on key terms "Inflammatory reactions", "Alzheimer's disease", "Inflammatory factors" and "Astrocytes" and Boolean operators. Articles before 2001 were removed.

**Results:** Finally, after analyzing the selected articles, 20 articles were extracted and included in this review.

**Conclusion:** Astrocytes are a group of glial cells in the central nervous system .The inflammatory activity of astrocytes plays a role in the development and progression of Alzheimer's disease. They strengthen the function of synapses by secreting neurotrophic factors. They also clear amyloid beta peptides from nerve tissue. Amyloid beta peptides bind to specific receptors on these cells and change the activity of these cells from anti-inflammatory to inflammatory type. It seems that astrocytes play a pivotal role in the development and progression of AD, particularly at the late stage of the disease. Finding a rational strategy to suppress inflammatory A1 phenotype might be a promising tool to slow down the progress of AD.

**Keywords:** Alzheimer's disease, Astrocytes, Inflammatory factors, Amyloid beta

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## Introduction

Alzheimer's disease (AD) is the most important and common neurodegenerative disease in the world. Global statistics state that in 2017, about 44 million people were affected by this disease. In the United States, AD is the only disease without a cure among the 10 leading causes of human death. In 2017, the costs paid in America for these patients were 259 billion dollars. It is predicted that by 2050, these costs can increase to an impressive figure of 1.1 trillion dollars (1, 2). This disease exists in two forms: early or familial and late sporadic (3). The late type affects individuals over 65 years old, and the early type includes a small number of affected people and occurs under 65 years of age (4). Currently, the amyloid beta hypothesis stands as the most accepted hypothesis which states that amyloid beta (Aβ) peptides are the early finding in the brain of affected people. Therefore, excessive accumulation of amyloid peptides in the form of amyloid plaques in the brain tissue disturbed neural connections and initiates neuro inflammation however, in normal brain Aβ is destroyed by various factors such as neprilysin, endothelin-converting enzyme, insulin-degrading enzyme, angiotensin-converting enzyme, plasmin and cathepsin D (5-8).

Other important symptoms of this disease include functional disorders of synapses, brain atrophy, and the creation of neuronal filament coils inside nerve cells, which consist of tau-hyperphosphorylated protein (1, 2).

Despite all the efforts made in the field of understanding this disease and the factors responsible for initiating AD, a suitable and guaranteed treatment has not yet been provided. Therefore finding a new strategy to control the disease and prevent its progression has great importance (9, 10).

## Materials and Methods

A complete and comprehensive search was conducted in the literature available in PubMed, Scopus, and Google Scholar databases, and articles were searched using the key terms "inflammatory reactions", "Alzheimer's disease", "inflammatory factors" and "astrocytes".

Key terms were selected using MeSH and Boolean operators such as "AND", "OR" and "NOT" were used to connect these terms. From October 2021 to December 2022, two researchers searched independently.

## Results

In this study, articles on Alzheimer's, inflammatory cytokines, memory, and astrocytes were selected. In the following, the articles that were presented about inflammatory diseases, brain, and depression, and also the articles before 2001 were removed. Also, to avoid excluding other valuable studies, a search was conducted to extract other related studies Abstract. Finally, 20 studies were extracted and included in this review.

## Discussion

Astrocytes are a group of glial cells present in the central nervous system (CNS) (11). These cells play important and different roles in the CNS. Perhaps their most important role is to initiate immune and inflammatory responses to prevent possible damage to nerve tissue. Astrocytes are the main regulators of magnesium concentration in the brain (11). Along with pre-synaptic and post-synaptic neurons, they are the main components of synapses and play a role in regulating synaptic plasticity by secreting gliotransmitter (12, 13).

**Astrocytic dysfunction results in the failure of Aβ clearance.**

The balance between the production and clearance of Aβ plays a detrimental role in AD, and an inefficient Aβ clearance may be more susceptible to AD (14). An increasing number of studies have evidenced that astrocytes act as a cellular player in Aβ clearance and degradation from the brain parenchyma into the perivascular space, across BBB (Figure 1), or by enzymatic degradation (15).

The BBB would be a diffusion barrier that impedes the influx into the brain parenchyma of certain molecules based on polarity and size. The principal cellular constituents of the BBB include capillary endothelial cells, perivascular pericytes, and astrocyte end-feet (Figure 1A). Maintaining the normal physiological

function of astrocytes will have a critical role in the transport of Aβ across BBB into the circulation which is mainly mediated by receptor for advanced glycation end products (RAGE) and lipoprotein receptor-related protein 1 (LRP1) in endothelial cells (16). Since RAGE acts as an important transporter via regulating the influx of circulating Aβ into the brain while the efflux of brain-derived Aβ into the circulation via BBB is implemented by LRP1 (14) (Figure 1B). In addition to the direct factor that astrocytic dysfunction leads to the failure transport of Aβ across BBB, astrocytic dysfunction may indirectly result in other avenues which are associated with the failure of Aβ clearance from the brain, such as abnormal interstitial fluid drainage and the failure of microglial phagocytosis (17). Astrocytic dysfunction probably induces the occurrence of neuroinflammation and oxidative stress, and then both neuroinflammation and oxidative stress contribute to abnormal interstitial fluid drainage and the failure of microglial phagocytosis, and the failure of Aβ clearance, finally (18).

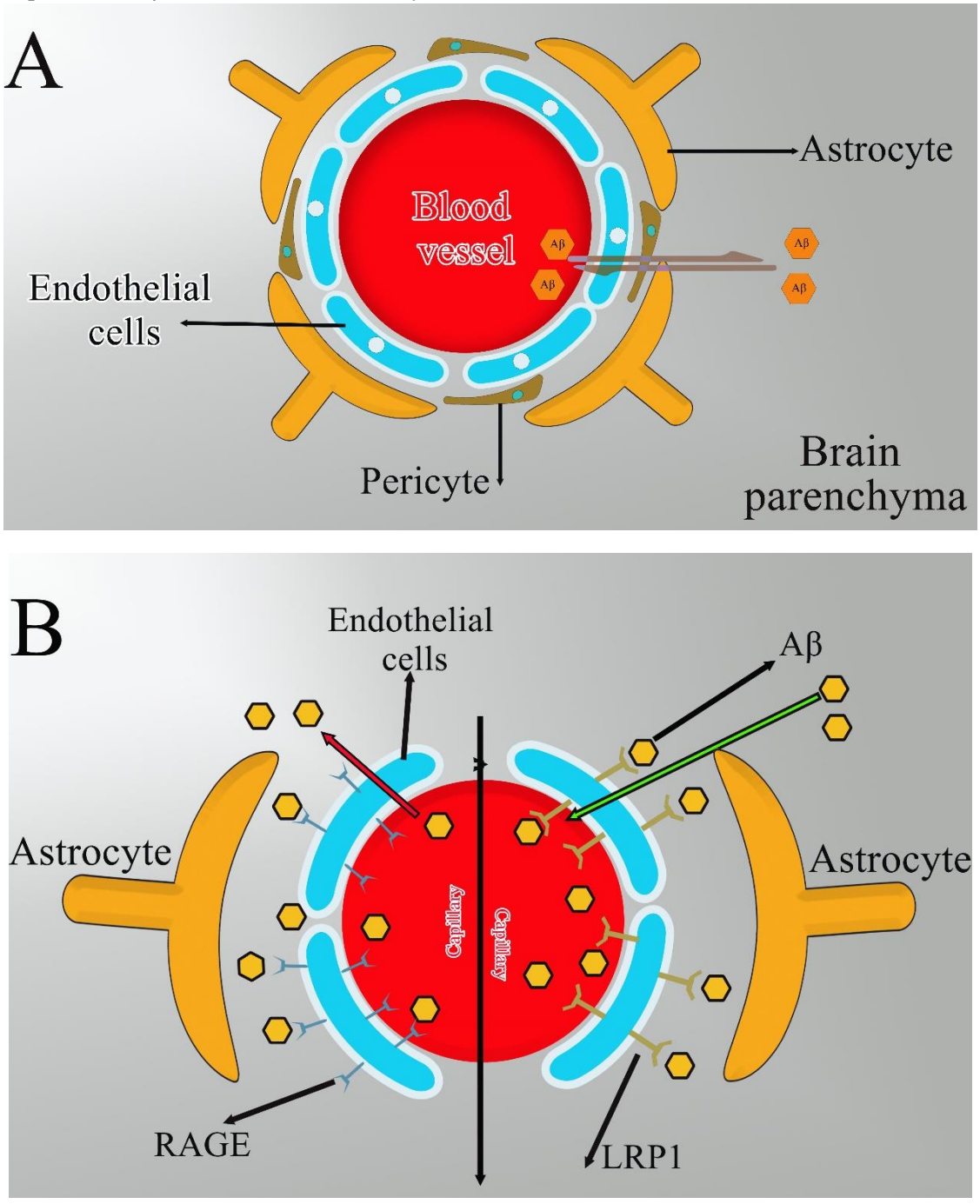


**Figure 1.** The proposed mechanism where astrocytes are associated with Aβ clearance).

**Major Roles of Astrocytes in Alzheimer´s Disease**

Alzheimer's disease (AD) is characterized by amyloid beta accumulation (Aβ or senile plaques), formation of hyperphosphorylated tau neurofibrillary tangles, neuroinflammation, synaptic demise, neuronal death, and brain dysfunction leading to severe cognitive impairment. The amyloid hypothesis originally postulated a linearity of progression according to Aβ accumulation, which subsequently led to the formation of tangles and other pathological hallmarks (19). The role of glial cells, and astrocytes in particular, in the neuropathology of many neurodegenerative diseases, is universally acknowledged (20).

The risk of AD is associated with genes mainly expressed by glial cells, either astrocytes, microglia, and/or oligodendrocytes (21).

Apolipoprotein E (APOE), a major genetic risk factor in Late-Onset AD (LOAD), is mainly expressed in astrocytes in the healthy brain (22) and contributes to the accumulation of Aβ in the brain (23).

Other genes associated with AD such as Clusterin (CLU) and Fermitin family member 2 (FERMT2) are similarly predominantly expressed by astrocytes. Reactive astrogliosis is prominent in AD being an early event in human patients and in animal models, possibly even preceding the formation of Aβ Aβ

plaques (24).

These data suggest a crucial role of astrocytes in the pathogenesis of AD. Morphological studies in post-mortem AD patient brains demonstrated close interaction between astrocytes and Aβ depositions (25).

It is however unclear how this close interaction translates into the disease progression. Astrocytes, when associated with senile plaques, become reactive with morphological hypertrophy manifested by thicker processes and increased expression of the intermediate filament proteins glial fibrillary acidic protein (GFAP), vimentin, nestin, and synemin (26).

Reactive astrocytes are found in both human AD patient brains [75] and AD mice models (27)

Pathological signals inducing astrogliosis in AD can be associated with damaged cells; Aβ by itself is a strong instigator of astrocyte reactivity. At the molecular level, Aβ induction of astrogliosis remodeling is mediated by $Ca^{2+}$ release from the endoplasmic reticulum; inhibition of the latter suppresses astrocytic reactivity (28).

In AD, astrocytes undergo relatively mild isomorphic gliosis and astrocytic domains do not overlap, potentially indicating a defensive nature of the astrocytic response. Indeed, inhibition of astrogliosis exacerbates Aβ accumulation and histopathology in AD mice (29). Reactive astrocytes in the vicinity of plaques display aberrant calcium dynamics (30).

In particular, human AD brains are characterized by severe disruption or even complete disappearance of interlaminar astrocytes (31). Atrophic astrocytes are characterized by reduced volume and thinner processes. In the 3xTg-AD mice model, atrophic astrocytes appear as early as 1 month of age in the entorhinal cortex (EC), and the atrophy is sustained after 12 months of age when Aβ plaques begin to appear (32).

Human astrocytes derived from induced pluripotent stem cells (iPSC) from patients with both familial and sporadic forms of AD also show atrophic phenotypes in vitro compared to control cells (33).

While atrophy might lead to loss of astrocyte homeostatic functions and give rise to synaptic dysfunction, increased excitability, and/or damage of the BBB, (Figure 2) very little functional data are available. Finally, the neurodegenerative process may directly damage astrocytes resulting

in clasmatodendrosis, characterized by fragmentation and disappearance of distal fine processes, along with swelling and vacuolation of the cell body (34) (Figure 2).

Astrocytes could be, in principle, involved in Aβ production as they upregulate β-secretase 1 and the amyloid precursor protein (APP) in the diseased brain (35).

However no quantitative data points to astrocytes as the major source of Aβ. Astrocytes are more likely to participate in Aβ clearance and elimination by different mechanisms. Astrocytes express aquaporin 4 (AQP4) water channels in their vascular end-feet and play an

essential role in the glymphatic system implicated in the clearance of Aβ (36) (Figure 2).

They also produce amyloid beta-degrading proteases that cleave the peptide into smaller fragments. The metalloendopeptidases neprilysin (NEP), insulin-degrading enzyme (IDE), and endothelin-converting enzymes 1 and 2 (ECE1 and ECE2) are all expressed in astrocytes and contribute to the degradation of monomeric Aβ species(37).

Astrocytes also express matrix metalloproteinases MMP-2 and MMP-9 which degrade both fibrillar and monomeric Aβ (37) (Figure 2).

Clearance of Aβ can be mediated by extracellular proteins APOE, ApoJ/Clusterin, β1-antichymotrypsin (ACT), and β-2-macroglobulin (β-2-M), all produced by astrocytes (Figure 2); these proteins promote the transport of β-2-macroglobulin Aβ across the BBB to the circulation either alone or in association with LRP1 and VLDLR receptors (37).

Recent studies report that iPSC-derived human astrocytes and mouse astrocytes expressing APOE4 are less efficient in clearing Aβ than those expressing APOE3 (38). Expression of APOE4 also leads to the degeneration of pericytes thus facilitating the breakdown of the BBB further contributing to cognitive impairment in APOE4 carriers (39). In AD, reactive astrocytes interact with neurons, microglia, and oligodendrocytes by releasing feed-forward signals and contributing to the vicious cycle that leads to neurodegeneration. Of note, β-2-macroglobulin β-2-macroglobulin Aβ can activate the NF- κ B pathway in astrocytes, which leads to the release of the complement protein C3 (Figure 2). The C3 binding to the microglial receptor C3aR alters β-2-macroglobulin -amyloid beta phagocytosis while the C3 binding to the neuronal receptor C3aR disrupts dendritic morphology and network function, both effects contributing to AD pathogenesis (40). Both NF- κB and C3 cascades are activated in the human AD brain and AD mouse models (41). About 60% of the astrocytes in the prefrontal cortex of AD patients are C3-expressing astrocytes (41) and could contribute to neuronal damage; although further analyses are needed for confirmation.

In AD, reactive astrocytes participate in shifting the excitation-inhibition balance through secretions of GABA. In a healthy brain, astrocytes do not contribute much to GABA production, however, in AD GABA starts to be synthesized by astrocytes through the putrescine-MAO-B pathway (42). In this way, reactive astrocytes start to secrete GABA thus increasing inhibition, likely to be a defensive response against neuronal hyperexcitability that seems to be a universal result of AD progression (43).

An increase in MAO-B expression in astrocytes, which accompanies AD, also results in a hyperproduction of hydrogen peroxide that may instigate neuronal damage and death (44) metabolic deficits (45) and mitochondrial dysfunction also contribute to AD progression (46). Extensive transcriptomics and proteomics studies revealed deficient mitochondrial bioenergetics in AD brains (47). Exposure of mouse astrocytes to Aβ up-regulates superoxide dismutase thus increasing oxidative stress (48); while the continuous infusion of Aβ into mice brains results in a substantial increase in the production of hydrogen peroxide (49) overproducing astrocytes has been recently detected in the brains of AD model mice (44). The toxic effect of Aβ on astrocytes is manifested by mitochondrial depolarisation with subsequent loss of $Ca^{2+}$ homeostasis (50). At the same time, astrocytes can exert neuroprotection at different stages of AD. Both astrogliosis and microgliosis in response to Aβ increase glial secretion of transforming growth factor (TGF-β) (Figure 2). TGF-β protects neurons from Aβ toxicity and enhances Aβ clearance by microglia (52). Moreover, astrocytes surrounding Aβ plaques demonstrate phagocytic activity and can phagocytose neuritic dystrophies in both mouse models and AD patients' brains, further suggesting the beneficial roles of astrocytes in AD (51). These data show that astrocytes actively contribute to the pathogenesis of AD. At the same time, many questions remain to be addressed. What astroglial states/phenotypes are found at different stages of AD? How do astrocyte states/phenotypes differ between brain regions, which are known to have different vulnerabilities to AD? How do astrocytes crosstalk with other brain cells? Are they able to promote neurodegeneration? How do AD risk genes modulate astroglial responses in AD? New methodologies such as RNA sequencing and spatial transcriptomics in combination with the use of human iPSC-derived

models and CRISPR-based studies are providing a deeper understanding of how astrocytes evolve during the course of AD.

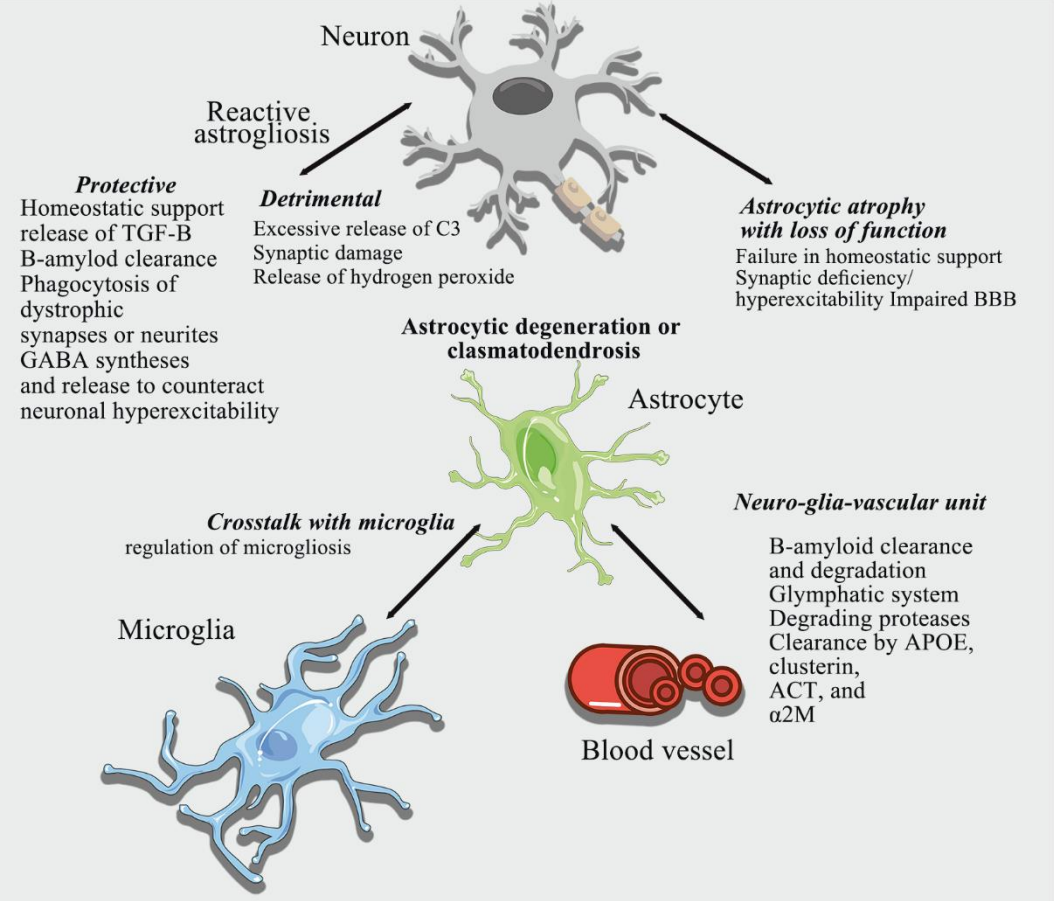


**Figure 2.** Contribution of astrocytes to Alzheimer´s disease.

By secreting neurotrophic factors such as tumor beta growth factor (TGF-β), brain-derived neurotrophic factor (BDNF), and neuron growth factor (NGF), astrocytes contribute to the growth of dendritic appendages and strengthen the function of the synapse (52) .They are also able to convert glucose into lactic acid and then, neurons use this lactic acid for pyruvate synthesis and metabolic functions (53). Astrocytes, possessing the enzyme glutamine synthetase, receive glutamate, which is the most important neurostimulator mediator in the CNS, and form part of the glutamine-glutamate cycle (54). Astrocyte mitochondria are concentrated near sites of homeostatic transport (50). These mitochondria provide energy for the $Na^+/K^+$ ATPase pump, which in turn causes the accumulation of neurotransmitters such as glutamate and regulates cytosolic $Ca^{2+}$ concentration (55). A deficiency in ATP supply may affect glutamate clearance and increase excitotoxicity. Mitochondrial dynamics and function are also impaired in human astrocytes with apolipoprotein E1 (APOE) allele (56).

In addition, there are some indications that astrocytic mitochondria can be transferred to neurons and contribute to neuronal bioenergetics. In particular, these processes seem to support neuroprotection after stroke (57). Studies show that astrocytic neuron transfer exerts neuroprotection in the context of Parkinson's disease (58).

Whether this process contributes to AD remains an exciting and unanswered question. Astrocytes seem to express lipoprotein E, neprilysin, insulin-degrading enzyme, endothelin-converting enzyme, angiotensin-converting enzyme, and matrix metalloproteinases, and clear Aβ peptides from nerve tissue (59). Recently the neuroprotective role of astrocytes also was reported (23, 24). They inhibited astrocytes in the AD model and reported that not only was cognition deficit exacerbated

but also neuroinflammation was apparent in their brain indicating the progress of AD in the absence of astrocytes (60).

However, it should be emphasized that astrocytes are a double edge sword playing both inflammatory (A1 type) and anti-inflammatory roles (A2 type). Considering diverse phenotypes of neurodegenerative A1 and neuroprotective A2 astrocytes, and the multidimensional functions of reactive astrocytes (41, 61), understanding the complete role of reactive astrocytes remains at the beginning of its path.

In a series of experiments, two groups of mice with certain characteristics were mated together. The first group was mice that had a gain-of-function mutation in the Aβ precursor protein (APP) gene and the other group was mice that lacked the NLPR3 inflammasome (a mediator molecule in the pathway inflammation related to receptors in astrocytes). Newborn babies showed better spatial memory compared to parents with mutations in APP, lower caspase 1 activity and more clearance of Aβ, and this itself can be proof of the role of astrocytes in the worsening of AD (52, 62).

Investigations show that Aβ peptides are connected to these cells through receptors located on the surface of astrocytes, and then the activity of these cells is changed to ward destruction and damage (52, 63-65).

One of the most important receptors and signaling involved here is the advanced glycation end products (RAGE/NF-κB) pathway, which is activated through the binding of Aβ to the RAGE receptor (56, 65). RAGE has two isoforms: the s-RAGE isoform, which is its soluble type, and the m-RAGE isoform, which is attached to the membrane and can have harmful effects in certain conditions, including bonding with Aβ (66).

The activation of this path causes the activation of a chain of molecular interactions in astrocytes and then in the entire nervous tissue. The nuclear factor kappa light chain enhancer of activated B cells (NF-κB) is a gene transcription complex that is normally inactively located in the cytoplasm. This complex generally consists of two parts. A regulatory part (in this case, called IκB) and an acting part (67). The binding of Aβ to RAGE, through the classical or canonical pathway, activates a kinase that phosphorylates the regulatory part of the NF-κB complex (IKK for short). This kinase, in turn, phosphorylates IκB and separates it from the complex and migrates into the cell nucleus, and promotes the transcription process of cytokine genes with the help of certain factors. Among these factors is bromodomain-containing protein 4 (BRD4). This protein is one of the three members of the benign essential tremors (BET) family. The members of this family share a sequence of about 110 amino acids called bromodomain (12, 67-69). In total, all these events cause the expression of specific inflammatory proteins and cytokines, and adhesion molecules in white blood cells. And in this way, astrocytes change from a neurotrophic state to a neurotoxic state (67).

In the field of various human diseases, numerous animal studies have been planned. Today, many specific animal models are used in medical research, including models of stroke (70), heart failure (71, 72), and kidney failure (73). In the field of mechanism, prevention, and treatment of Alzheimer's disease, many animal studies have been used, for example, the study conducted by Nikkar et al (60) simultaneous administration of bromodomain and histone deacetylase I inhibitors alleviates cognition deficit in Alzheimer’s model of rats .

Among the most important inflammatory cytokines that are secreted, all types of interleukins (ILs) such as IL-1β, IL-6, IL-10, IL-17, IL-18, tumor necrosis factor (TNF-α), interferons (IFNs) especially IFN-γ and chemokines such as Monocyte chemoattractant protein (MCP) and macrophage inflammatory protein (MIP) noted (74, 75).

The release of these cytokines causes neutrophils and macrophages to be called, neurons to be damaged, dendritic spines to be destroyed, and synapse dysfunction, resulting in cognitive defects. The binding of these cytokines to their receptors in neurons causes the activation of mediators such as protein kinase C (PKC), caspase 1, caspase 3, p38 and pathways such as phosphoinositide 3-kinases, caspase 3 activity alone is sufficient to trigger the events leading to neuronal apoptosis. Caspase 3 can also cause abnormal processing of tau protein so that this protein is broken at the place of aspartate 421 root and a product is created that accumulates faster than the natural form of tau in the neuron and shortens the life of the neuron (76, 77).

In addition, these cytokines can affect the 5'-UTR region of the APP gene, causing its overexpression and eventually increasing Aβ (78).

They can also cause the activation of beta and gamma-secretase enzymes in the path of APP amyloidogenic processing and regularly increase the production and secretion of Aβ (79). In response to amyloid beta, calcineurin protein is activated in astrocytes and this causes the activation of a transcription factor called a nuclear factor of activated T-cells (NFAT) in this way, the production and secretion of cytokines will increase (52). By binding to their receptors on the surface of astrocytes, Aβ, and IL-1 can induce the production of sphingomyelinase enzyme in astrocytes. The substrate of this enzyme is sphingomyelin found in cell membranes, and by breaking it down, it produces ceramide, which is a secondary messenger and induces messages related to the death of neurons and even astrocytes themselves (80, 81). IL-1β increases the phosphorylation of tau protein and decreases a pre-synaptic marker called synaptophysin through the p38-MAPK pathway in primary culture media containing neurons and astrocytes (82).

IL-18 can affect N-methyl-D-aspartate (NMDA) receptors and thereby interfere with the long-term potentiation (LTP) process (81). NMDA receptors affect tau protein structure and function in different ways (81). For example, signals generated by these receptors can activate calpains. Calpains stimulate tau phosphorylation by affecting other kinases such as glycogen synthase kinase, cyclin-dependent kinase 5 (CDK5), extracellular signal-regulated kinases (ERK1), and ERK2. Calpain activity also cleaves p35 to p25 and.p35 normally forms a CDK5/p35 complex with cyclin-dependent kinase 5 (CDK5) and this complex phosphorylates tau protein to its normal level. but p25 aggravates this process and tau hyperphosphorylation (81, 83, 84). The research of Farman and his colleagues showed that in APP/PS1 mice, by using the Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT) peptide, which is an interfering factor in the Calcineurin/NFAT[2] pathway, it is possible to reduce the activity of astrocytes as well as the level of Aβ, and the function of synapses and indicators (62). Improve learning and memory (59).

Garwood and his colleagues concluded experiments that using the antibiotic minocycline can prevent the activity of astrocytes and prevent the activation of caspase 3 in neurons and the production of h-tau. Additionally, they were able to demonstrate that adding Aβ to culture media containing both neurons and astrocytes induced neuronal death more rapidly than media containing only neurons. In this way, they clarified the role of astrocytes and inflammation in Alzheimer's pathogenesis (63). In 2004, Bergamaschini and colleagues showed that the use of enoxaparin (a type of low molecular weight heparin) in Alzheimer's mice reduced the number of active astrocytes surrounding amyloid plaques and slowed the progression of the disease (85). Henka and his colleagues showed that the use of pioglitazone and ibuprofen reduces inflammation in glial cells and also reduces the amount of Aβ1-42 in APPV717I transgenic mice (86).

Medeiros and his colleagues showed that the long-term use of IL-1 receptor-blocking antibodies in 3xTg Alzheimer's mice improves cognitive deficits, reduces the damage caused by tau protein, and reduces certain types of Aβ filamentous and oligomeric peptides (87).

In 2017, Yi and his colleagues showed that Boldin, which is extracted from the boldo tree, is effective in improving the condition of Alzheimer's mice by inhibiting the activity of connexins in glial cells, including astrocytes (88).

In 2015, Zhang and colleagues showed that the use of paeoniflorin as an anti-inflammatory in Alzheimer's APP/PS1 mice reduced the activity of glycogen synthase kinase and it also prevents the chain of inflammatory processes in the NF-κB pathway and excessive activation of astrocytes (68). Fragoulis and his colleagues showed that the use of methysticin, an activator of the Nuclear factor E2-related factor 2 (Nrf2) pathway (which is an anti-inflammatory transcription factor), in the form of oral gavage during 6 months with a weekly dose of APP/Psen1 Alzheimer's mice, it reduces astrogliosis, inflammatory cytokines secretion and reduces long-term memory disorders (89).

In 2018, Wilkanik and his colleagues showed that intraperitoneal injection of roscovitine in Alzheimer's

mice prevented CDK5 activity and the process of inflammatory responses (90). Astrocytes, when associated with senile plaques, react with morphological hypertrophy manifested by thickening processes and increased expression of the intermediate filament proteins glial fibrillary acidic protein (GFAP), vimentin, and nestin (87).

These data show that astrocytes are actively involved in the pathogenesis of AD. At the same time, many questions remain to be addressed. What are the astroglial states/phenotypes in different stages of AD? How do astrocytic states/phenotypes differ between brain regions with different vulnerabilities to AD? How do astrocytes communicate with other brain cells? Are they able to detect neurodegenerative disorders? How do AD risk genes modulate astroglial responses in AD?

It is hoped that new methods such as RNA sequencing and spatiotemporal transcription, in combination with human induced pluripotent stem cells (iPSC)-derived models and clustered regularly interspaced short palindromic repeats (CRISPR) based studies, will provide a deeper understanding of how astrocytes evolve during AD (Table 1).

**Table 1.** Summary of the research conducted on the role of astrocytes and inflammatory mediators in the development of Alzheimer's disease).

| The name of the scholar | Year | Reference | Type of Study | Results |
|---|---|---|---|---|
| Furman et al | 2012 | (62) | Using the VIVIT peptide Calcineurin/NFAT pathway interfering factor) in APP/PS1 mice. | The activity of astrocytes and the level of amyloid beta decreased, and the function of synapses and learning and memory indicators improved. |
| Garwood et al | 2011 | (63) | Conducting tests using the antibiotic minocycline. | It prevented the activity of astrocytes and prevented the activation of caspase 3 in neurons and the production of hyperphosphorylated tau. |
| Garwood et al | 2011 | (63) | Comparison of the addition of amyloid beta to vessel media containing neurons and astrocytes with media containing only neurons. | Amyloid beta-induced neuronal death more quickly and revealed the role of astrocytes and inflammation in Alzheimer's pathogenesis. |
| Bergamaschini et al | 2004 | (85) | Application of Enoxaparin (a type of low molecular weight heparin) in Alzheimer's rats. | Reducing the number of active astrocytes surrounding amyloid plaques and reducing the speed of disease progression |
| Heneka et al | 2005 | (86) | Pioglitazone (PPARγ agonist) and ibuprofen were used. | Reduction of inflammation in glial cells and reduction of Aβ1-42 in APPV717I transgenic mice. |
| Garwood et al | 2011 | (63) | Use of minocycline antibiotic in h-tau mice | Reducing the activity of astrocytes and preventing the activation of caspase 3 in neurons and the production of h-tau protein (hyperphosphorylated tau) |
| Medeiros et al | 2011 | (87) | Long-term use of IL-1 receptor blocking antibody in 3xTg Alzheimer's mice. | Improvement of cognitive deficits, reduction of damage caused by tau protein, and relative reduction of certain types of amyloid beta filamentous and oligomeric peptides. |
| Furman et al | 2012 | (62) | Using the peptide VIVIT, an interfering agent in the Calcineurin/NFAT pathway in APP/PS1 mice. | It reduced the activity of astrocytes as well as the level of amyloid beta and improved the function of synapses and memory. |

| | | | | |
|---|---|---|---|---|
| Zhang et al | 2015 | (81) | Using Paeoniflorin as an anti-inflammatory in APP/PS1 Alzheimer's mice | Preventing the activity of glycogen synthase kinase enzyme as well as the chain of inflammatory processes in the path of NF-κB and excessive activation of astrocytes. |
| Yi et al | 2017 | (88) | Preventing the activity of connexins of glial cells and including astrocytes with the help of Boldine, which was obtained from the Boldo tree. | In improving the disease condition in Alzheimer's mice. |
| Fragoulis et al | 2017 | (89) | Using methysticin by oral gavage for 6 months with a dose of once a week in APP/Psen1 Alzheimer's mice. | It reduced astrogliosis, reduced the release of inflammatory cytokines, and reduced long-term memory disorders. |
| Wilkaniec et al | 2018 | (90) | Intraperitoneal injection of Roscovitine in Alzheimer's rats. | It prevents the activity of CDK5 (cyclin-dependent kinase 5) and the process of inflammatory responses |
| Nikkar et al | 2022 | (60) | Chronic co-inhibition of astrocytes metabolism (with fluorocitrate) and also BRD4 (with JQ1) on cognition deficit at early stages of AD in rats. | Inhibition of astrocytes metabolism by fluorocitrate impaired spatial memory and reduced CREB/PSD95/synaptophysin levels in the hippocampus |

## Conclusions

Astrocytes have multiple functions in the brain and are essential for protecting neurons and maintaining homeostasis .However, under different pathological conditions including AD, they are associated with loss of function associated with neuroinflammation and neurodegeneration. A thorough characterization of these cellular states, together with morphological and functional analyses, will enhance the understanding of how astrocytes evolve in pathology .Soon, using selective inhibitors for A1 or A2 types of astrocytes, we may be able to correlate different astroglial states with specific stages of Alzheimer's disease and clarify the exact role of these cells in various stages of AD.

### Author contribution

All the authors met the standard writing criteria based on the recommendations of the International Committee of Medical Journal Editors and all contributed equally to the writing of the work.

### Conflict of interest

The authors hereby declare that there is no conflict of interest regarding the present research.

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