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REVIEW

Astrocytes in depression and Alzheimer's disease

Yang Liao[1], Qu Xing[2], Qianqian Li[3], Jing Zhang[1], Ruiyuan Pan (✉)[1], Zengqiang Yuan (✉)[1]

[1]*The Brain Science Center, Beijing Institute of Basic Medical Sciences, Beijing 100850, China;* [2]*School of Life Sciences, Zhengzhou University, Zhengzhou 450001, China;* [3]*School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China*

Abstract **Astrocytes are an abundant subgroup of cells in the central nervous system (CNS) that play a critical role in controlling neuronal circuits involved in emotion, learning, and memory. In clinical cases, multiple chronic brain diseases may cause psychosocial and cognitive impairment, such as depression and Alzheimer's disease (AD). For years, complex pathological conditions driven by depression and AD have been widely perceived to contribute to a high risk of disability, resulting in gradual loss of self-care ability, lower life qualities, and vast burden on human society. Interestingly, correlational research on depression and AD has shown that depression might be a prodrome of progressive degenerative neurological disease. As a kind of multifunctional glial cell in the CNS, astrocytes maintain physiological function via supporting neuronal cells, modulating pathologic niche, and regulating energy metabolism. Mounting evidence has shown that astrocytic dysfunction is involved in the progression of depression and AD. We herein review the current findings on the roles and mechanisms of astrocytes in the development of depression and AD, with an implication of potential therapeutic avenue for these diseases by targeting astrocytes.**

Keywords astrocytes; depression; Alzheimer's disease; roles; mechanisms

Introduction

Astrocytes are identified as versatile glial cells and closely associated with other cell types in the brain. The conventional wisdom of astrocytes is "brain glue," which means that astrocytes were thought to function as a neuronal supporting matrix [1,2]. However, emerging evidence suggested that the function of astrocytes is far from supporting cells. They can interact with neurons and form tripartite synapses, playing a crucial role in maintaining stable neuronal function, including the regulation of extracellular fluid, ion homeostasis, ion transportation, cerebral blood flow, synaptic remodeling, and energy supply [3–6]. In addition, the endfeet of astrocytes together with vascular endothelial cells maintains the integrity of the brain–blood barrier (BBB) and provides a homeostatic environment for the brain [7]. Moreover, astrocytes can interact with microglia to respond to brain injury, bacterial infection, and other insults in the brain. The interplay between astrocytes and microglia always couples in many neuroinflammatory diseases, including depression and Alzheimer's disease (AD) [8].

As a common chronic disease, depression is characterized by specific symptoms in human mental, emotional, and physical health such as sadness, low self-esteem or guilt, sleep disturbance, tiredness, attention deficit, and anhedonia [9–11]. Generally, symptoms of depression develop gradually, and patients frequently have an intention to self-injure or even commit suicide. Epidemiological studies have indicated that the prevalence of depression has increased over the past decades; depression has been estimated to affect more than 300 million people globally, nearly 4.4% of the world's population [12,13]. According to the World Health Organization reports, depression was ranked as the third cause of the global burden of disease and was expected to rank first by 2030 [14]. Unfortunately, the pathogenesis of depression is still unclear. Several hypotheses have been proposed to explain its pathogenesis. Among them, the monoamine neurotransmitter serotonin (5-hydroxytryptamine (5-HT)) hypothesis is the most widely investigated and appreciated [15]. 5-HT is synthesized from the essential amino acid tryptophan and produces physiologic effects by binding

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Correspondence: Ruiyuan Pan, panruiyuan168@sina.com;
Zengqiang Yuan, zyuan620@yahoo.com

with seven broad families (5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, 5-HT7 receptor families) [16]. The 5-HT hypothesis affirmed that imbalance of 5-HT levels and dysfunction of 5-HT receptor families are involved in depression [17,18]. The significant functions of 5-HT in modulating normal neuronal development and excitability have already been proved [19,20]. Nevertheless, these speculations remain controversial. The diagnosis and treatment of depression are still a challenge to clinicians due to the uncertain pathogenesis.

AD is the most common degenerative disease in the elderly and is characterized by progressive cognitive impairment [21]. With the acceleration of the global aging population, the number of patients with AD is rapidly increasing. More than 100 million people worldwide are predicted to suffer from AD by 2050 [22–25]. However, the pathogenesis of AD remains unclear. The primary hypotheses of AD are the amyloid-β (Aβ) cascade hypothesis and tau protein hypothesis. The Aβ cascade hypothesis proposes that the accumulation of Aβ results from the imbalance of Aβ production and clearance. Subsequently, Aβ accumulation caused by either Aβ overproduction or Aβ clearance impairment would finally rise to neurotoxicity [26–28]. The tau protein hypothesis postulates that tau protein hyperphosphorylation leads to neurofibrillary tangles (NFTs) and subsequent neuron loss [29,30].

Although the pathogenesis of depression and AD is mainly based on hypotheses, both diseases have many similarities. Interestingly, mounting evidence suggested that depression may be a risk factor or even a prodrome of AD [31–33]. Postmortem studies and other medical investigations showed that abnormal morphological and functional astrocytes appear in the development of depression and AD [34–37]. Therefore, we propose that astrocytes may be involved in the pathogenesis of these two diseases, and restoring astrocytic homeostasis would be a new avenue for treating them.

Astrocytes in depression

Astrocytes regulate energy metabolism in the development of depression

Normal energy metabolism is essential for neuron network homeostasis. Generally, neurons consume 80%–90% of total energy in the central nervous system (CNS) [38]. The neuronal energetic substrates, glucose and lactate, mainly stem from capillaries and astrocytes and are delivered through glucose transporters (GLUTs) and monocarboxylate transporters (MCTs), respectively [39–41]. Precisely, lactate produced in astrocytes can instantly deliver abundant energy to satisfy the neuronal requirements [40,42]. Astrocytes take up glucose from surrounding capillaries via GLUT1 and store it in the form of glycogen. By contrast, neurons are weak in energy storage [43]. They release glutamate during neuronal transmission to stimulate glycogen catabolism, aerobic glycolysis, and lactate production in nearby astrocytes, and then astrocytes release lactate via MCT1 or MCT4 [44,45]. This process is named astrocyte–neuron lactate shuttle (ANLS) and is posited to support neuronal plasticity and excitability [43,46–50].

Emerging evidence demonstrated that metabolism disorder is involved in the pathogenesis of depression [51]. Experiments conducted in mice exhibited temporary increases in extracellular lactate in the brain when mice were exposed to the forced swimming test. These lactates were found to be derived from astrocytes and involved in neuronal excitability and synaptic plasticity [52]. We can regard this phenomenon as an instant energy compensation to neuronal stress, which verifies the function of rapid energy supply about lactate [53]. Carrard *et al*. have increased hippocampal lactate levels through peripheral administration of lactate, which induced antidepressant-like effects. The injection of lactate downregulates glycogen synthase kinase-3β (GSK-3β) and cAMP response element binding protein (CREB) phosphorylation, which is akin to the effect of certain antidepressant drugs such as lithium [54]. Lactate upregulates synaptic plasticity-related genes such as activity-regulated cytoskeletal protein (Arc), c-fos, and Zif268 [55] (Fig. 1). Lactate administration also amplifies 5-HT signaling by increasing p11 (a binding protein for a 5-HT receptor) and increases the expression of astrocyte marker S100β [54]. These results indicate that astrocytes may be a mediator of the antidepressant-like effects of lactate by regulating 5-HT receptor trafficking [54,56]. Subsequently, experiments carried out by Karnib *et al*. also verified the antidepressive effects of lactate. Similar to Carrard *et al*., they applied peripheral injection of lactate to mice susceptible to chronic social defeat stress (CSDS), strengthening resilience and rescuing social avoidance behavior and anxiety in mice [57].

There are still controversial opinions on the ANLS hypothesis because it lacks direct evidence of lactate transportation from astrocytes to neurons. For example, the cellular location of lactate consumption in the brain remains unclear, and neurons also use other approaches to obtain energy besides MCTs, such as glucose transport systems [58,59]. Notwithstanding, astrocyte-derived lactate is indispensable for neuronal energy consumption and plasticity [43]. Even though neurons can use glucose as a direct energy source, astrocyte-derived lactate is predominantly required to maintain normal physiologic activities [40]. Together, as an energy substrate, astrocyte-derived lactate is a significant mediator and potential target for treating depression.

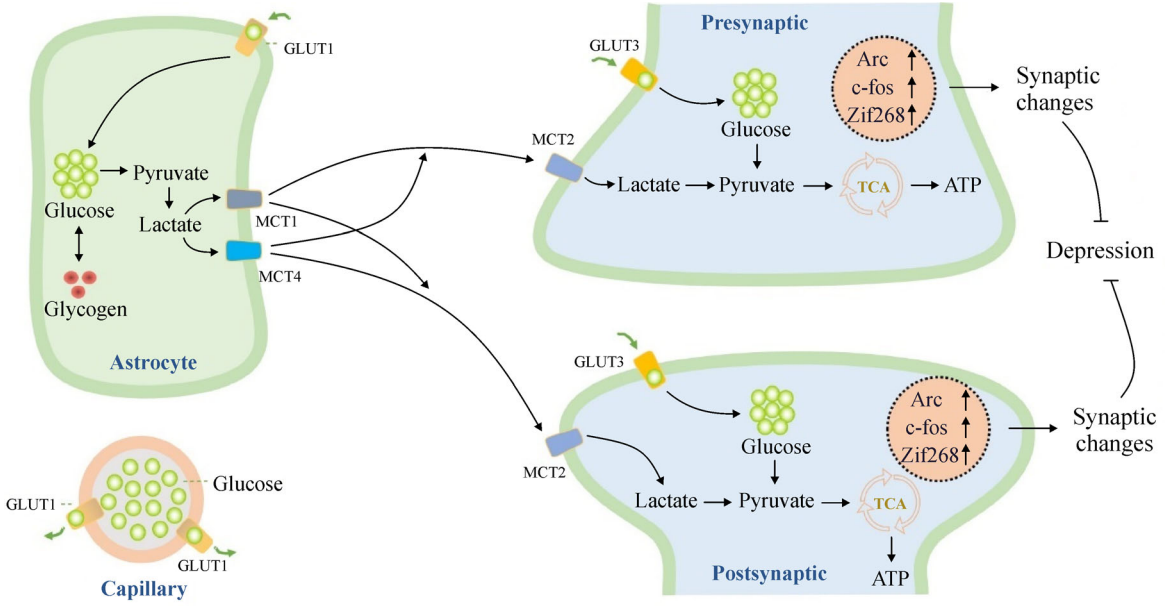

Fig. 1 Diagram of ANLS in depression. Astrocytes take up glucose from the capillary via GLUT1, store it by converting it into glycogen, or catabolize it into pyruvate by glycolysis. Pyruvate can be converted into lactate, which is then delivered into neurons through MCTs. The uptake of astrocyte-derived lactate by neurons is converted to pyruvate. Glucose from the capillary can also be absorbed in neurons via GLUTs and is then catabolized into pyruvate, which is fed into the TCA cycle for energy production and participates in synaptic plasticity and depression development. MCTs, monocarboxylate transporters; GLUT, glucose transporter; TCA, tricarboxylic acid cycle.

Astrocyte-derived adenosine 5′-triphosphate (ATP) is associated with depression

ATP, a multifunctional molecule, was initially recognized as an energy transfer medium [60]. However, recent studies revealed that ATP plays vital roles not only in neuronal energy metabolism but also in neuronal plasticity. Notably, ATP serves as a gliotransmitter or neuromodulator to modulate functional neuronal homeostasis when the extracellular concentration of ATP is low in normal conditions. P2XR-mediated ATP energetic transmission has been found in CNS synapses [61,62]. Correspondingly, insufficient ATP results in impaired synaptic plasticity in the progression of depression [63–67]. Vesicular ATP released from astrocytes is a significant source of extracellular ATP in the brain to maintain neuronal function [63,68]. Cao *et al*. found that the ATP level was remarkably decreased in the prefrontal cortex (PFC) in CSDS model mice. Accordingly, the regional injection of ATP into the medial PFC (mPFC) produced an antidepressant-like effect without impacting murine locomotor activity. Moreover, Cao *et al*. concluded that ATP binding with P2X2R in the mPFC is required for the antidepressant role of ATP [63]. Astrocytic exocytosis of ATP can also govern neuronal dopamine (DA) release in developing depression-like syndrome [69]. Taken together, astrocyte-derived ATP acts as a neuromodulator to modulate depressive-like behaviors.

In addition to the vesicular ATP-releasing mechanism, researchers are eager to search the specific ATP-releasing channel proteins. CALHM1/2, two calcium homeostasis modulator (CALHM) family proteins, contain four-pass transmembrane domains and recently have been identified as an ATP-releasing channel [70–74]. Ma *et al*. found an apparent reduction of astrocytic ATP release in CALHM2 knockout mouse [72]. Deficiency of ATP release alters spine morphology and plasticity, which induces depressive-like syndrome in mice [72,75]. Furthermore, similar phenotypes were observed in the astrocyte-specific CALHM2 deficiency mice, further supporting that CALHM2 regulates depression-like behaviors as an astrocytic ATP-releasing channel [72].

However, an apparent increase in extracellular ATP in the brain, mainly derived from dead cells and reactive astrocytes, is associated with pathological changes (such as stress and cellular injury) [76,77]. Moreover, these ATPs non-selectively bond with microglial P2X7 receptor (P2X7R), which leads to the efflux of K^+, thereby inducing NLRP3 inflammasome assembly, caspase-1 stimulation, and cytokine interleukin-1 (IL-1β) maturation and release [78,79]. Therefore, treatment with P2X7R antagonists, elimination of NLRP3, or blockade of peripheral IL-1β could rescue depression caused by chronic stress [78,80,81]. Furthermore, ATP has been reported as a “danger signal” or a “warning molecule” in the brain, which interacts with purinergic receptors such as P2X7R, P2Y1R, and A2AR in brain disorders [82,83].

Overall, astrocytic ATP plays important roles in

neuronal function, which might be involved in depression (Fig. 2). On the one hand, homeostatic astrocytes maintain physiologic levels of extracellular ATP, which supports neuronal viability and synaptic plasticity. On the other hand, reactive astrocytes release excessive ATP into the extracellular matrix and subsequently activate nearby microglia through the P2X7 receptor, resulting in the activation of the NRLP3 inflammation and thus neurotoxicity. Therefore, ATP is an important mediator that connects astrocytes and depression. Although the mechanisms of ATP involvement in the development of depression remain to be explored, we can conclude that astrocyte-derived ATP in low level and physiologic dose is fundamental for maintaining normal physiologic function.

Astrocyte-mediated neuroinflammation modulates depressive-like syndrome

Brain immunity depends on astrocytes and microglia due to the BBB. Astrocytes, together with microglia, regulate the immune system in the brain and escort BBB function. Neuroinflammation is usually regarded as the activation of astrocytes and microglia, both of which switch to a state of pro-inflammation to release a vast number of pro-inflammatory cytokines [84,85]. In addition to ATP-mediated neuroinflammation that has been described above, astrocytes participate in regulating various inflammatory signal transductions. There are several signaling pathways of astrocyte-mediated neuroinflammation, such as gp130, TGFβR, IFNγR, ERα, A20, STAT3, FasL, and BDNF; the upregulation of these signaling pathways in astrocyte is usually recognized as an anti-inflammatory response; on the contrary, the activation of Act1, S1P1, B4GALT6, TrκB, NF-κB, SOCS3, CCL2, CXCL10, or VEGF signaling pathways is a pro-inflammatory effect [86]. Therefore, astrocytes are a "double-edged sword" in the case of neuroinflammation, performing detrimental and protective functions. Astrocyte ablation has been shown to cause severe neuroinflammation in experimental autoimmune encephalomyelitis (EAE) or brain injury in mice [87–89]. However, another study showed that astrocyte depletion improved neuroinflammation in the chronic phase of EAE [90]. Whether astrocytes play a beneficial or a detrimental role depends on their state. Astrocyte activation is the main cause of neuroinflammation.

Depression is commonly accompanied by neuroinflammation, which causes the activation of microglia and astrocytes, lessens brain serotonin, activates the hypothalamic–pituitary–adrenal axis, and impairs synaptic plasticity and neurotransmission [91–94]. In rodent models, lipopolysaccharide (LPS) is frequently adopted to induce depression-like behaviors by producing severe neuroinflammation [95–98]. Specifically, Leng *et al.* discovered that the expression of multiple endocrine neoplasia type 1 (Men1; protein: menin) is decreased in the brain of mice subject to chronic unpredictable mild

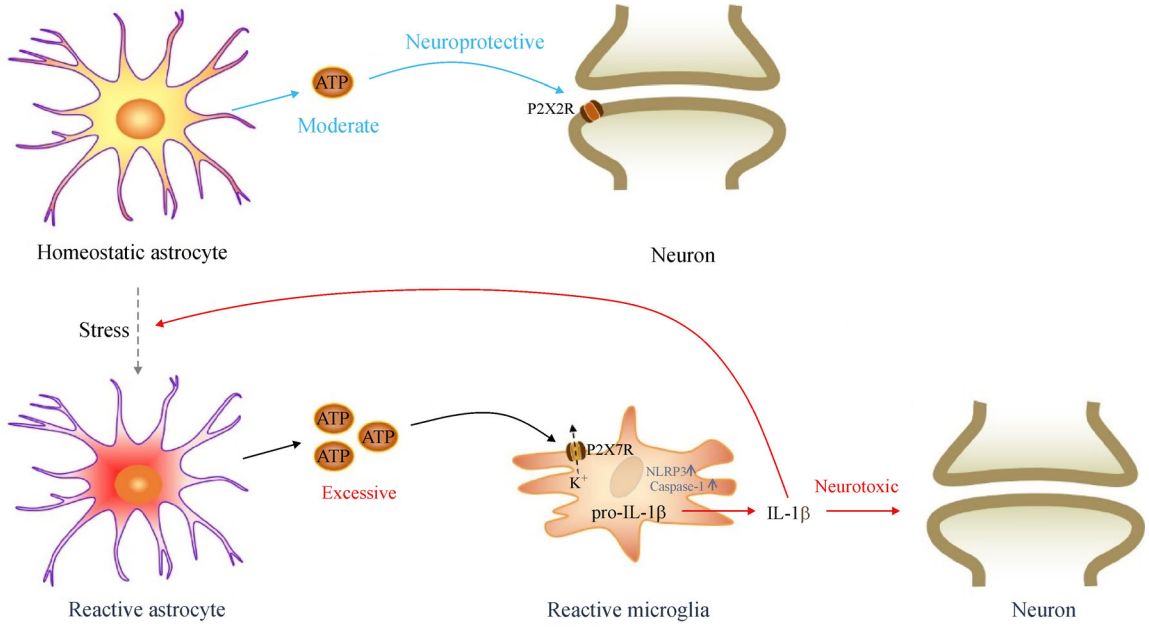

Fig. 2 Astrocyte-derived ATP plays a dual role in neuronal function. Due to the significantly different receptor affinities in normal circumstances (P2X2 is100-fold > P2X7), ATP released from homeostatic astrocytes serves as a neurotransmitter or neuromodulator, which binds with P2X2R in neurons, maintaining neuronal morphology, excitability, and plasticity. By contrast, when astrocytes are activated under pathological conditions, they produce excessive ATP, binding with P2X7 in microglia, followed in sequence by the upregulation of NLRP3 and caspase-1, release of IL-1β, and finally neuroinflammation and neurotoxicity.

stress and LPS-induced neuroinflammation. Moreover, they found that astrocyte-specific menin deficits promote NF-κB-induced IL-1β upregulation, resulting in morphological abnormalities and synaptic deficits in neurons and depression-like behaviors in mice. Interestingly, they found an association between MEN1 mutations and major depressive disorder risk in humans [99]. Other studies also supported the view that astrocyte-mediated neuroinflammation is involved in depression pathology. LPS-induced astrocyte activation can cause depression-like behaviors, which can be alleviated by inhibiting astrocyte reaction [100–102].

Taken together, neuroinflammation is a crucial link or even a prerequisite in the progression of depression. Thus, neuroinflammation can be regarded as a standing point to seek antidepression strategies. Specifically, reducing astrocyte activation might be a considerable approach.

Astrocytes in AD

Astrocytes are closely involved in amyloid pathology

Being abundant in the CNS, the role of astrocytes in AD has received less attention and appreciation compared with microglia [103]. However, along with the recognition of the connection between astrocytes and AD, astrocytic roles in the development and progression of AD are attracting more attention.

During the progression of AD, Aβ originates from amyloid precursor protein (APP) and plays a central role in AD pathogenesis. APP is cleaved by beta-site APP cleaving enzyme 1 (BACE1), which yields sAPPβ and a cell-membrane-bound fragment (C99). Then, C99 is cleaved by γ-secretase, which releases Aβ and amyloid intracellular domain. Aβ aggregation was thought to be the significant event that drives the progression of AD pathology, which mainly exists in the extracellular matrix in the brain, followed by glial reaction, neuroinflammation, neurotoxicity, neuronal cell death in the hippocampus and gray matter, and eventually memory impairment and dementia [104–106].

Post-mortem AD brain tissue analysis has shown that reactive astrocytes are accumulated around Aβ deposits [107–109]. After exposure to Aβ, similar to microglia, astrocytes are polarized to the A1 status and subsequently release cytokines (such as IL-1β or IL-6), nitric oxide, reactive oxygen species, and excessive glutamate [110–113]. The series of neurotoxicity or excitotoxicity eventually evolves into neuron loss and neurodegeneration. Furthermore, the expression of BACE1 was found in astrocytes, which indicates that astrocytes may be involved in Aβ aggregation [114]. To identify the astrocytic source of Aβ, Veeraraghavalu *et al*. dissociated primary astrocytes from the brains of newborn PS1ΔE9flox or APPswe mice and 8-week-old APPswe/PS1ΔE9flox mice. They detected the expression of Aβ secreted by astrocyte in a culture medium, which could be prevented by the treatment of γ-secretase inhibitor [115]. Taken together, it would be a vicious cycle accelerating disease progression: Aβ induces reactive astrocytes, and then reactive astrocytes, in turn, promote Aβ aggregation and AD pathogenesis.

Astrocytes influence tau protein accumulation in AD progression

Microtubule has been verified to be a vital component of neuronal cytoskeleton protein, involved in nutritional support of neuronal bodies and axons. As an effective form of microtubule-associated proteins, tau is a critical component of a microtubule. Moreover, tau has crucial physiologic functions in modulating microtubule, including microtubule polymerization and stabilization and its normal structural function. However, hyperphosphorylated tau aggregates can cause NFT generation, microtubule dysfunction, and finally neuronal death, which are the significant pathologies of AD [116–118].

In addition to neuronal tau accumulation, astrocytic tau accumulation also exists and plays a pivotal role in AD pathology [119,120]. Current evidence indicated that 3R isoforms of tau rather than 4R tau are responsible for tau aggregation [121,122]. Specifically, Richetin *et al.* have proved that the accumulation of 3R tau in hilar hippocampal astrocytes is related to AD severity in individuals [123]. Astrocyte-specific overexpression of 3R tau impairs normal mitochondrial distribution and functions in hilar astrocytes and disturbs the hippocampal neuronal network *in vivo*, which in turn damage hippocampal function. Correspondingly, mice with astrocytic 3R tau accumulation exhibit a spatial memory deficit [123]. Moreover, hyperphosphorylated tau aggregates are promoted by senescent cell accumulation, which drives neurodegenerative disease, while removing senescent glial cells, including astrocytes and microglia, could attenuate tau phosphorylation [124]. Therefore, astrocytic tau protein or astrocyte-promoting tau accumulation plays an essential role in tau pathology during the development of AD, indicating that astrocytes could be a crucial target in AD treatment. Hence, the underlying mechanism of astrocytes in tau pathogenesis needs to be systematically studied.

Astrocytes impact AD progression via regulating energy metabolism, extracellular ATP release, and neuroinflammation

Akin to depression, ANLS impairment can also be observed in the progression of AD [56,125]. A recent study demonstrated that expressions of MCTs (MCT1, MCT2, and MCT4) and lactate-relevant enzymes (lactate

dehydrogenase A) are decreased in the cortex and hippocampus of APP/PS1 mice [126]. Suzuki *et al*. also reported that disruption of MCT1, MCT2, or MCT4 expression impairs synaptic plasticity and long-term memory, while recovery of lactate transport between astrocytes and neurons can rescue these defects [49]. Intriguingly, ATP has been shown to control Aβ aggregation in AD progression [127]. Jung *et al*. showed that astrocyte-derived ATP might prevent neuronal plasticity impairment and dendritic spine loss in the pathology of Aβ [128].

In addition, astrocyte-mediated neuroinflammation is involved in AD [129–133]. Alleviation of astrocytic reaction driven by adeno-associated virus ameliorates Aβ pathology, modulates synaptic plasticity, and improves cognition in AD model mice [134]. Interestingly, Katsouri *et al*. demonstrated that ablation of astrocytes increases Aβ levels, affects synaptic and neuronal density, and induces memory deficits in mice [135]. These studies indicated the crucial role of astrocytes in inflammation-related diseases, including AD. Maintaining normal astrocytic function and decreasing its activation might prevent the occurrence of AD.

Astrocytes, a promising therapeutical target for depression and AD

Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) and DA agonists might exert neuroprotective effects through astrocytes [136–138], given that astrocytes express 5-HT receptors (e.g., 5-HT1A and 5-HT7), glial serotonin transporter (SERT), and dopaminergic receptors (e.g., D1R and D2R) [139–142]. For example, SSRIs and tricyclic antidepressants can downregulate the expression of astrocytic neurotransmitter transporters, such as SERT, leading to the increased level of 5-HT [143,144]. Interestingly, fluoxetine (a typical SSRI) can target astrocytes and increase the release of BDNF in hippocampal astrocytes and extracellular ATP level *in vivo* [145]. Other antidepressants such as imipramine and paroxetine can also upregulate BDNF mRNA expression in a primary culture of hippocampal astrocytes [145]. Moreover, treatment with antidepressants can significantly change the BDNF and glial cell line-derived neurotrophic factor (GDNF) level in patients with depression [146]. BDNF and GDNF are two nutritional factors mainly derived from glial cells, which play an important role in the survival and function of midbrain DA neurons, and might be involved in the progression of depression [147,148]. In addition, DA can bind with astrocytic D1, mediating excitatory synaptic regulation [142]. The activation of the astrocytic dopamine 2 receptor can suppress neuroinflammation in the CNS [139]. Altogether, these findings indicated that antidepressant drugs could execute their pharmacological effects not only directly on neurons but through regulating astrocytes. Interestingly, these mentioned drugs or molecules might have effects on depression and AD.

SSRIs, which are typically administered as antidepressant drugs, have been shown to reduce Aβ deposition in AD mice and patients [149]. Specifically, fluoxetine administration can improve spatial learning and memory functions in AD mice by mitigating hippocampal neuron loss, decreasing Aβ level, inhibiting GSK-3β activity, and upregulating the level of β-catenin [150,151].

DA, an excitability-related neurotransmitter, is downregulated or dysfunctional in depression [152,153]. DA receptor agonists such as aripiprazole and cariprazine can effectively alleviate depressive symptoms [154]. Interestingly, DA receptor expression is lower in AD individuals [155,156]. Accordingly, DA agonists could restore synaptic plasticity in AD patients [157]. Similar to SSRIs, a dopaminergic system-relevant therapeutic strategy has been proposed as a potentially effective treatment for AD [157–159].

Taken together, numerous pathophysiological mechanisms mediated by astrocytes are involved in depression and AD; in other words, astrocytes are a potential linker between depression and AD as they are involved in the development of both diseases, indicating that astrocytes might be a potential therapeutic target for the treatment of depression and AD.

Conclusions and perspectives

This review collected and summarized evidence to show how astrocytes participate in the development of depression and AD (Fig. 3). On the one hand, as a kind of multifunctional glial cells, homeostatic astrocytes secrete a range of factors, including ATP, BDNF, and growth factors, maintaining neuronal viability and synaptic plasticity. On the other hand, pathogenic astrocytes release toxic factors that promote cell death or cytokines and chemokines that cause neuroinflammation [160,161]. Mounting evidence has suggested that astrocytes are actively involved in various neuropathological processes, including depression and AD.

We herein conclude that astrocytes modulate energy metabolism, extracellular ATP, and neuroinflammation in the progression of depression. Concurrently, astrocytes also govern the above processes and Aβ aggregation and tau protein accumulation in the pathology of AD. The dysfunction of astrocytes in depression and AD implies a correlation between depression and AD. Interestingly, both diseases share numerous similar epidemiological characteristics in addition to similar molecular and pathological changes. For example, depression is regarded as a risk factor or even a prodrome for AD [31,162,163].

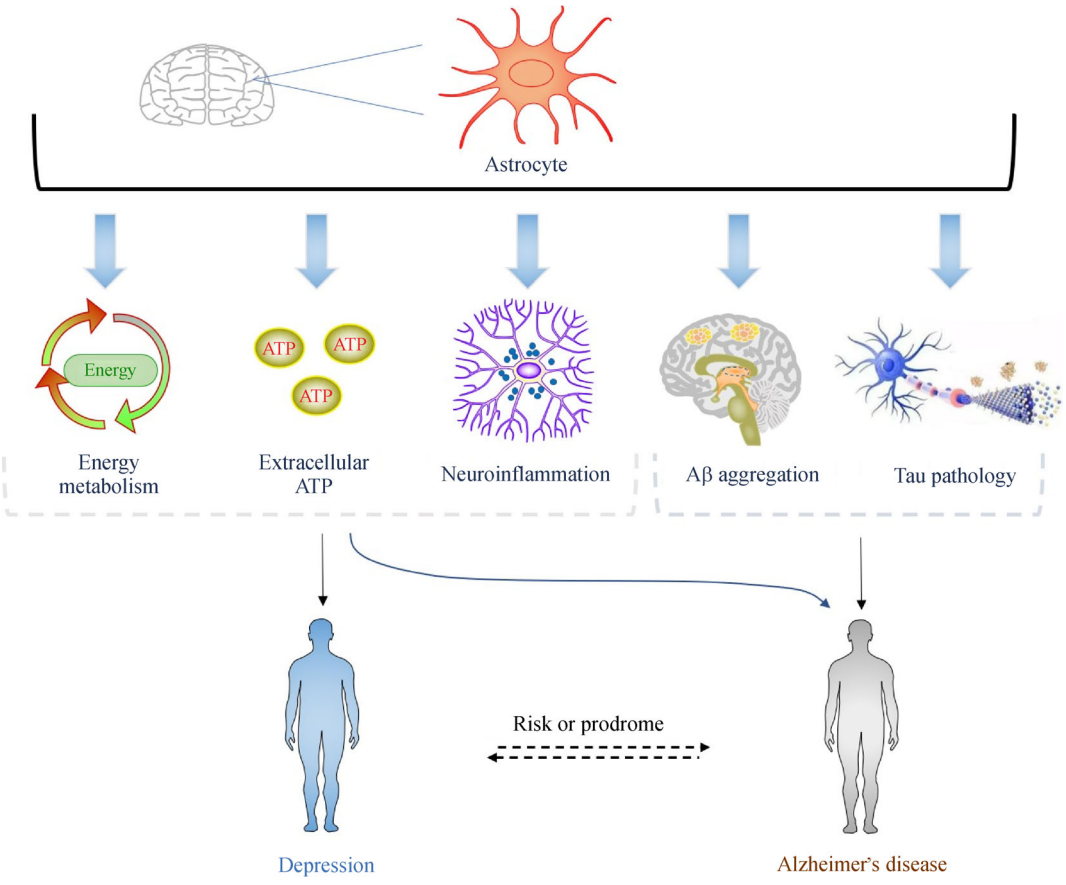

Fig. 3 Summary of this review. Astrocytes modulate extracellular ATP, neuroinflammation, and energy metabolism in the progression of depression. In addition, astrocytes regulate the above physiologic processes and Aβ aggregation and tau protein hyperphosphorylation in the pathology of AD. The multiple roles of astrocytes in depression and AD might link depression and AD. Increasing evidence showed that depression is thought to be a risk factor or prodrome of AD. Aβ, amyloid-β.

Furthermore, depression increases the risk of heart disease, stroke, and neuroinflammation, all of which are regarded as high-risk factors of AD [164–166]. Although mounting evidence has presented both relationships in a clinical setting and basic research, direct evidence showing that early depression causes AD is still lacking. Therefore, the relationship between depression and AD remains to be further investigated.

Importantly, the diagnosis and treatment of depression and AD remain challenging. The current drugs are insufficient to cure both diseases because of inadequate treatment outcomes and unpredictable side effects [167]. We herein propose a possible treatment of these two diseases by targeting astrocytes. For example, focal transplantation of healthy astrocytes in the brain has been proposed to be a promising therapeutic method for depression [168]. The engraftment of astrocytes producing a neuroprotective effect and cognitive enhancement has been verified in a rodent model [169,170]. Recently, Zhou *et al*. and Qian *et al*. found that efficient astrocyte–neuron conversion by genome editing to generate new neurons in the mouse brain can replenish the lost neuron in neurodegenerative disease. This method was demonstrated to alleviate motor dysfunctions in mice with Parkinson's disease [171,172]. Thus, genome editing-induced astrocyte–neuron conversion might also be a promising therapeutic method for neurodegenerative disease, including AD. Taken together, given the multiple functions of astrocytes in depression and AD that have been reviewed above, we argue that targeting astrocytes to maintain their functional homeostasis would be a potential strategy for treating these diseases.

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Compliance with ethics guidelines

Yang Liao, Qu Xing, Qianqian Li, Jing Zhang, Ruiyuan Pan, and Zengqiang Yuan declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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