Epilepsy therapy beyond neurons: Unveiling astrocytes as cellular targets

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From the Contents

Abstract

Epilepsy is a leading cause of disability and mortality worldwide. However, despite the availability of more than 20 antiseizure medications, more than one-third of patients continue to experience seizures. Given the urgent need to explore new treatment strategies for epilepsy, recent research has highlighted the potential of targeting gliosis, metabolic disturbances, and neural circuit abnormalities as therapeutic strategies. Astrocytes, the largest group of nonneuronal cells in the central nervous system, play several crucial roles in maintaining ionic and energy metabolic homeostasis in neurons, regulating neurotransmitter levels, and modulating synaptic plasticity. This article briefly reviews the critical role of astrocytes in maintaining balance within the central nervous system. Building on previous research, we discuss how astrocyte dysfunction contributes to the onset and progression of epilepsy through four key aspects: the imbalance between excitatory and inhibitory neuronal signaling, dysregulation of metabolic homeostasis in the neuronal microenvironment, neuroinflammation, and the formation of abnormal neural circuits. We summarize relevant basic research conducted over the past 5 years that has focused on modulating astrocytes as a therapeutic approach for epilepsy. We categorize the therapeutic targets proposed by these studies into four areas: restoration of the excitation–inhibition balance, reestablishment of metabolic homeostasis, modulation of immune and inflammatory responses, and reconstruction of abnormal neural circuits. These targets correspond to the pathophysiological mechanisms by which astrocytes contribute to epilepsy. Additionally, we need to consider the potential challenges and limitations of translating these identified therapeutic targets into clinical treatments. These limitations arise from interspecies differences between humans and animal models, as well as the complex comorbidities associated with epilepsy in humans. We also highlight valuable future research directions worth exploring in the treatment of epilepsy and the regulation of astrocytes, such as gene therapy and imaging strategies. The findings presented in this review may help open new therapeutic avenues for patients with drug-resistant epilepsy and for those suffering from other central nervous system disorders associated with astrocytic dysfunction.

Key Words: astrocyte; cellular microenvironment; drug resistance; epilepsy; excitability; homeostasis; metabolism; neural networks; neuroinflammation; neuron

Introduction

Epilepsy is a prevalent and disabling neurological disorder that affects individuals of all ages; it is characterized by recurrent and unprovoked seizures and is often accompanied by stereotypical abnormal behaviors, with or without impaired awareness (Fisher et al., 2017; Jia et al., 2024; Liu et al., 2024). Globally, the estimated number of patients with epilepsy ranges from 50 to 70 million, with an annual increase of 2.4 million (Trinka et al., 2019). The economic burden of epilepsy accounts for approximately 0.5% of the global disease burden (Picard, 2022), and according to an analysis from the Global Burden of Disease Study in 2016, epilepsy resulted in approximately 18.3 million disability-adjusted life years lost (Hu et al., 2021). Antiseizure medications are the primary treatment for newly diagnosed epilepsy, with more than 20 antiseizure medications available that target voltage-gated ion channels or restore neurotransmitter balance (Löscher et al., 2020). However, approximately one-third of patients continue to experience seizures despite receiving appropriate medical treatment (Chen et al., 2018). For patients with drug-resistant epilepsy, nonpharmacological treatments include epilepsy surgery, neural modulation techniques, and a ketogenic diet, providing alternative therapeutic options (Wang et al., 2021; Medina-Pizarro et al., 2023). However, their clinical utilization is limited by substantial knowledge gaps, high costs, and complexities (Khoo et al., 2021). Additionally, current neuron-targeted therapies provide only temporary seizure control without disease-modifying effects, let alone a cure. Patients are required to adhere to a strict daily medication regimen to prevent unpredictable epileptic episodes. Unfortunately, these medications often carry significant toxicity and the risk of developing drug resistance. Hence, exploring therapeutic strategies that target nonneuronal cells represents a promising avenue for more effective epilepsy treatments.

Astrocytes, one of the most abundant types of glial cells in the mammalian brain (Lee et al., 2022; He et al., 2024; Zhang et al., 2024), perform a multitude of physiological functions. These cells directly interact with endothelial and adjacent cells to maintain the structural integrity and permeability of the blood–brain barrier (BBB) (Liao et al., 2024), facilitate neurovascular coupling, and regulate blood flow, thereby providing metabolic support to neurons (García-Cáceres et al., 2019; Manu et al., 2023). As integral components of

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tripartite synapses, astrocytes modulate the levels of extracellular neurotransmitters, such as glutamate and gamma-aminobutyric acid (GABA), as well as ions and water (Li et al., 2021). They also influence pH levels and release gliotransmitters, thereby contributing to synaptic transmission and neuronal excitability. Considerable clinical and preclinical data suggest that the dysregulation of astrocyte functions plays a significant role in seizures and epileptogenesis (Vezzani et al., 2022). Reactive astrocytes, which undergo structural and metabolic changes, are key drivers of neuroinflammation. Disruption of the glial cell-mediated regulation of ions, water, and neurotransmitters can facilitate hyperexcitability and hypersynchrony (Devinsky et al., 2013; Guo et al., 2022). Uncontrolled glial cell-mediated immunity can induce sustained inflammatory changes, thereby promoting the occurrence of epilepsy (Liu et al., 2023).

Emerging preclinical studies have shown promising outcomes for epilepsy intervention or modification via the regulation of astrocyte function (Chen et al., 2023b; Guan et al., 2024; Qiu et al., 2025). First, numerous studies have aimed to restore the excitation–inhibition balance by reshaping the functions of astrocytes in synapse modulation (Nguyen et al., 2020; Lezmy et al., 2021). The accumulation of the excitatory neurotransmitter glutamate at synapses can increase neuronal excitability (Peterson and Binder, 2020). To mitigate this, researchers have attempted to suppress the degradation or increase the expression of glutamate transporters to relieve excessive synaptic glutamate (Gao et al., 2017; Sha et al., 2017). Second, by targeting the astrocyte–neuron lactate shuttle, lactate dehydrogenase (LDH) inhibitors have been found to block excess energetic transport from astrocytes to neurons, thereby attenuating neuronal hyperactivity (Sada et al., 2015). Similarly, an identified dysfunctional astrocytic phenotype in epilepsy, called lipid-accumulated reactive astrocytes, has been recognized as a novel prospective target for regulating epilepsy by restoring lipid metabolism (Chen et al., 2023b). Third, astrocytes actively participate in inflammation and immune microenvironment remodeling in epilepsy. The soluble molecules released by activated glial cells include cytokines, glutamate, adenosine triphosphate, $NH4^+$, and amyloid-β (Cornell-Bell et al., 1990; De Bastiani et al., 2023; de Ceglia et al., 2023). Glial cell-mediated inflammation resulting from various brain injuries can promote seizure initiation and epileptogenesis, particularly when normal feedback mechanisms fail to limit and resolve inflammation. Chronic uncontrolled astrocyte activation is associated with excessive release of proinflammatory molecules, disruption of the BBB accompanied by serum albumin influx, and the formation of glial scars (de Rus Jacquet et al., 2023). Initial preclinical and clinical studies suggest that certain anti-inflammatory drugs have therapeutic effects on drug-resistant epileptic seizures (Radu et al., 2017; Vezzani et al., 2019). By modulating neuroinflammation, repairing damaged neural tissue, and promoting the regeneration and reconstruction of disrupted neural circuits, astrocytes offer a potential therapeutic pathway for restoring brain function in epilepsy patients (Zhao et al., 2024). Targeting astrocyte dysfunction could become a promising strategy to enhance neural regeneration and restore normal neural network function in epilepsy, potentially reducing seizures and mitigating long-term damage caused by excessive neuronal excitation.

The understanding of the dysfunctional roles of astrocytes and their potential as therapeutic targets in epilepsy has gradually increased over the past several decades (**Figure 1**). In this review, we discuss how astrocyte dysfunction, disrupted cellular metabolism, neuroinflammation, and aberrant neural circuits contribute to epileptogenesis and seizures. We highlight contemporary strategies targeting astrocyte dysfunction in epilepsy management, which are structured into four key components: restoring the excitation–inhibition balance, reestablishing metabolic homeostasis within the neuronal microenvironment, modulating immune and neuroinflammatory homeostasis, and reconstructing neural circuits. This review aims to provide new insights and strategies for disease modification and treatment of epilepsy through astrocyte modulation.

Search Strategy

We conducted a comprehensive search in the PubMed database, covering articles published from 2000–2024, using the following Medical Subject Headings (MeSH) terms: ("Astrocytes" [Mesh] AND ("Neuronal metabolism" [Mesh] OR "Neuroinflammation" [Mesh] OR "Neural circuits" [Mesh])) AND ("Epilepsy" [Mesh] OR "Drug Resistant Epilepsy" [Mesh]) AND ("Treatment" [Mesh] OR "Therapeutics" [Mesh]). Title and abstract screening focused on studies exploring the role of astrocytes in epilepsy development and astrocyte–neuron crosstalk in metabolism, neural circuits, and neuroinflammation. While our search covered a broad time frame, we prioritized recent literature published between 2019 and 2024, particularly those pertinent to the section "Targeting Astrocytes for Epilepsy Therapy." Key earlier studies and reviews of significant relevance were also included.

Astrocytes: Functionality Under Physiological Conditions

Astrocytes originate from neural progenitor cells in the subventricular zone and migrate to all regions of the central nervous system (CNS) through their radial glial processes. Since being first described by Virchow (1858) in the 1980s, astrocytes have gained considerable attention. They exhibit diverse and complex functions, playing critical roles in normal physiological functions as well as in diseased states. The following paragraph provides a brief summary and review of the physiological functions of astrocytes, focusing on four areas: maintaining the excitation/inhibition balance, preserving neuronal microenvironment homeostasis, controlling neuroinflammation, and regulating neural circuits (**Figure 2**). Astrocytes closely interact with neurons to regulate synaptic transmission, impacting both excitatory and inhibitory synapses. By managing neurotransmitter release and uptake, astrocytes influence the activity of GABAergic interneurons, which are essential for maintaining inhibitory control (Fiacco and McCarthy, 2004). They also play a key role in maintaining the homeostasis of ions, particularly potassium (Kofuji and Newman, 2004). During neuronal activation, astrocytes absorb excess extracellular potassium, preventing neuronal depolarization and preserving electrical stability. Additionally, they regulate glutamate levels through uptake and recycling, preventing excitotoxicity and stabilizing the neuronal microenvironment. Astrocytes are critical for regulating neuroinflammation and act as sentinels that release cytokines and chemokines in response to inflammatory signals (Reid and Kuipers, 2021). Depending on the situation, they can either suppress or enhance inflammation, offering neuroprotection against pathogens or trauma. However, prolonged activation may lead to harmful chronic inflammation. Furthermore, astrocytes modulate neural circuits by adjusting synaptic strength and plasticity, particularly through mechanisms such as long-term potentiation and depression (Henneberger et al., 2010). Through gliotransmitter release, astrocytes influence neuronal activity and connectivity, supporting the development and function of the neural circuits essential for cognition and behavior (Perea and Araque, 2007).

Reactive Astrocytes Under Epileptic Conditions

Reactive astrogliosis is a prominent feature of

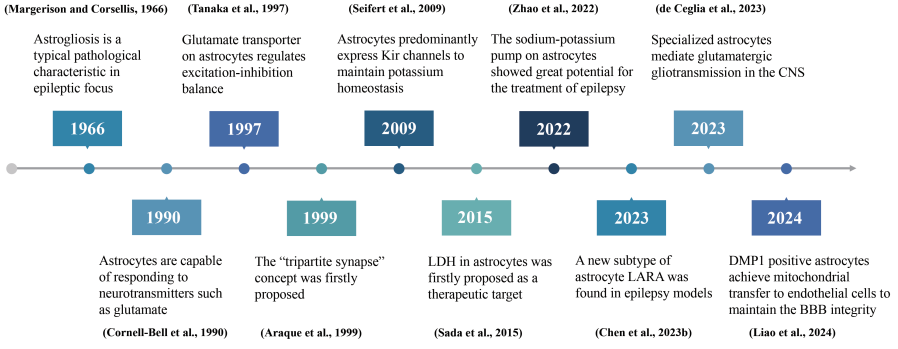

Figure 1 | **A timeline illustrating the progressive deepening of our understanding of the dysfunctional roles of astrocytes and their potential as therapeutic targets in epilepsy in the literature.**
BBB: Blood–brain barrier; CNS: central nervous system; DMPI: dentin matrix protein 1; Kir: inward-rectifier potassium channel; LARA: lipid-accumulated reactive astrocyte; LDH: lactate dehydrogenase.

chronic focal epilepsy (Margerison and Corsellis, 1966) and is characterized by the hypertrophy of cell bodies and processes, as well as the upregulation of specific proteins, particularly glial fibrillary acidic protein (Patel et al., 2019). Increased proliferation of reactive astrocytes has been observed in specimens from epilepsy patients and animal models (Boison, 2012; Sano et al., 2021). However, some studies have indicated that spontaneous seizures in mouse models can be induced by widespread chronic astrogliosis through conditional deletion of β1-integrin (Robel et al., 2015; Schiweck et al., 2021). Therefore, determining whether astrocyte proliferation is a cause or a consequence of epilepsy onset has become challenging. However, reactive astrocytes, due to molecular, metabolic, and functional changes under pathological conditions, clearly contribute to the development of epilepsy. The following discussion focuses on the relationship between reactive astrocytes and the onset and development of epilepsy, emphasizing how astrocytes fail to maintain the excitatory–inhibitory balance and metabolic homeostasis in the pathological microenvironment (**Figure 3**).

Inducing imbalance in neuronal excitation and inhibition

Astrocytes have been recognized as crucial participants in CNS synapses for two decades since the "tripartite synapse" concept was first proposed (Araque et al., 1999; Blanco-Suárez et al., 2017). During brain development, astrocytes play a role in inducing the formation, elimination and maturation of neuronal synapses through multiple mechanisms (Brandebura et al., 2023). In the mature brain, astrocytes also regulate the excitatory–inhibitory balance by clearing neurotransmitters and releasing gliotransmitters. In glutamatergic synapses, astrocytes efficiently take up extracellular glutamate released during neural impulses via sodium-coupled excitatory amino acid transporters. Once inside astrocytes, glutamate is predominantly converted to glutamine via the glutamine synthetase pathway. Glutamine is subsequently released into the interstitial space and taken up by neurons for glutamate synthesis, completing the glutamate–glutamine cycle. Increased extracellular glutamate is a biochemical hallmark of epilepsy (**Figure 3**) and has been reported in both animal models and epilepsy patients (Kanamori and Ross, 2011; Sarlo and Holton, 2021). Under normal physiological conditions, astrocytes are responsible for rapidly clearing the surge of glutamate in the synaptic cleft after an excitatory event. However, during epilepsy, the loss of glutamine synthetase and downregulation of excitatory amino acid transporters contribute to the failure of glutamate control (Tanaka et al., 1997). Glutamine synthetase converts glutamate to glutamine, which is subsequently transported into inhibitory neurons to be converted into GABA or into excitatory neurons where it can be reverted to glutamate (Vezzani et al., 2022). In a comparative study of hippocampal sclerosis and nonsclerosis samples from temporal lobe epilepsy patients, van der Hel et al. (2005) reported more pronounced neuron loss and reduced glutamine synthetase enzyme activity in hippocampal sclerosis samples. Another study by Eid et al. (2004) revealed that the loss of glutamine synthetase was particularly evident in regions of the mesial temporal lobe epilepsy hippocampus where reactive astrocytes aggregated. The downregulation of glutamate transporter 1 (GLT-1) has been demonstrated in many studies, contributing to the dysregulation of the astrocytic clearance of glutamate (Hubbard et al., 2016; Peterson and Binder, 2020). These findings suggest an impaired capacity of astrocytes to process glutamate in epileptic foci.

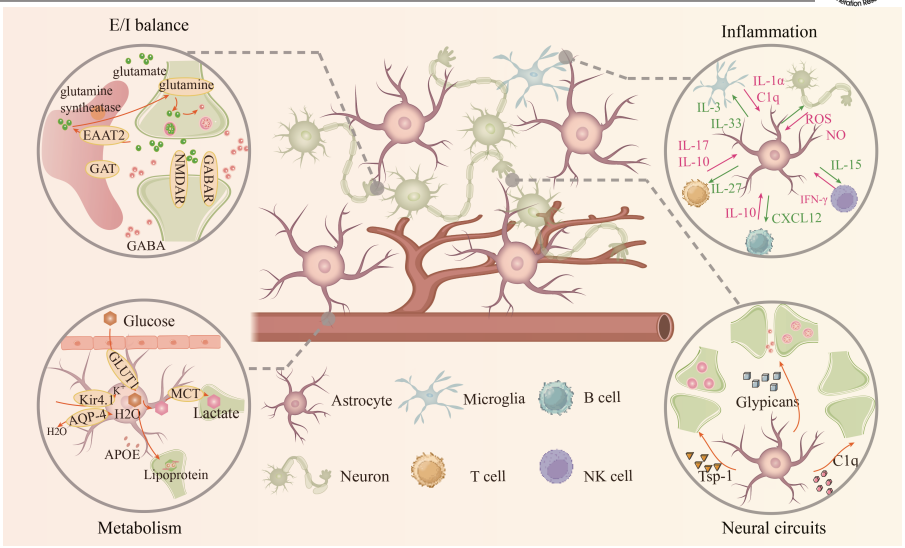

Figure 2 | **Astrocytes play crucial roles in maintaining physiological functions in the brain.**
Their roles include regulating the excitation–inhibition balance by controlling glutamate and GABA levels; maintaining neuronal microenvironmental homeostasis by managing the metabolism of water, ions, lipids, and lactate; modulating central nervous system immunity and inflammation through interactions with immune cells; and participating in the formation and function of neural circuits. APOE: Apolipoprotein E; AQP-4: aquaporin-4; CXCL: chemokine ligand; EAAT 2: excitatory amino acid transporter 2; E/I: excitation-inhibition; GLN: glutamine; GABA: gamma-aminobutyric acid; GLUT 1: glucose transporter 1; GLU: glutamate; GS: glutamine synthetase; IL: interleukin; Kir 4.1: inwardly rectifying potassium channels 4.1; MCT: monocarboxylate transporters; NO: nitric oxide; ROS: reactive oxygen species; TSP: thrombospndins.

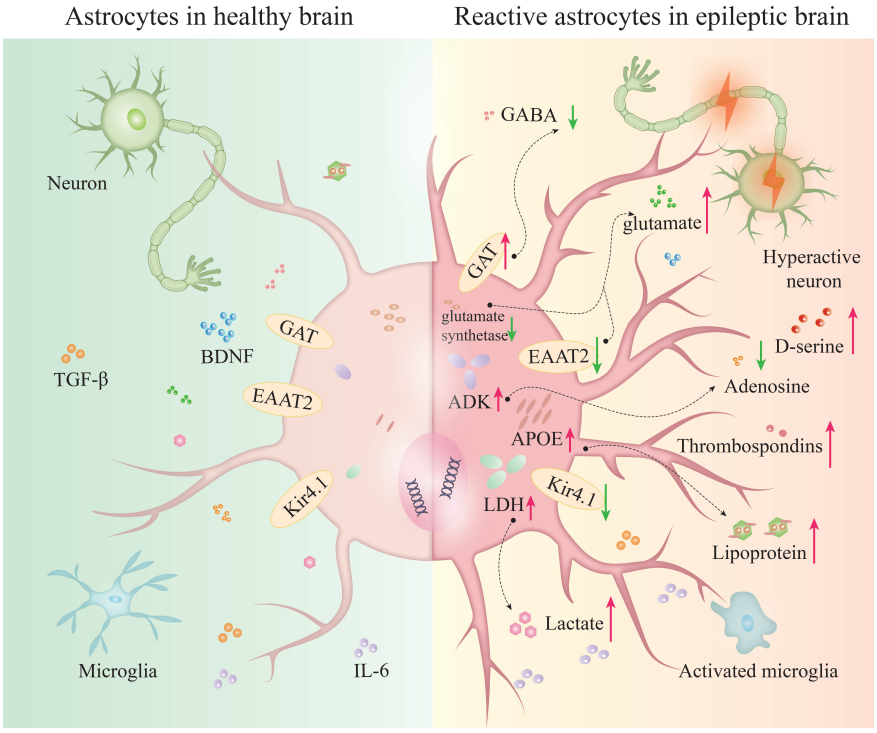

Figure 3 | **Reactive astrocytes play a pivotal role in epileptogenesis.**
In epilepsy, astrocytes undergo morphological and functional abnormalities, leading to increased neuronal excitability (red arrows represent upregulation, and green arrows represent downregulation). ADK: Adenosine kinase; APOE: apolipoprotein E; BDNF: brain-derived neurotrophic factor; EAAT2: excitatory amino acid transporter 2; GAT: gamma aminobutyric acid transporter; GABA: gamma-aminobutyric acid; GLU: glutamate; GS: glutamine synthetase; IL: interleukin; Kir 4.1: inwardly rectifying potassium channels 4.1; LDH: lactate dehydrogenase; TGF-β: transforming growth factor-β.

Like fast neurotransmitters, adenosine triphosphate, which is an endogenous ligand for purinergic receptors, has the potential to directly mediate synaptic transmission (Zhang et al., 2003). Additionally, astrocyte-derived adenosine triphosphate triggers microglial activation through the activation of P2X7 and/or P2Y1 receptors, leading to the release of cytokines that activate astrocytic receptors (Brough et al., 2002). The adenosine triphosphate released from astrocytes can be broken down by ectonucleotidases into adenosine. This adenosine then attaches to A1 receptors on both presynaptic and postsynaptic neurons, resulting in a reduction in presynaptic transmitter release and postsynaptic excitability (Weltha et al., 2019). Adenosine plays crucial roles in various physiological functions in the CNS, such as sleep, arousal, neuroprotection, learning and memory, and cerebral blood circulation (Bynoe et al., 2015). The extracellular levels of adenosine are regulated by adenosine kinase, which is expressed primarily in astrocytes (Boison, 2016). In epilepsy, adenosine is widely recognized as an endogenous anticonvulsant due to its A1 receptor-mediated synaptic inhibition and neuroprotective effects (Patel et al., 2019). Dysregulation of adenosine kinase expression can limit adenosine levels, compromising its antiepileptic and neuroprotective properties (**Figure 3**). Interestingly, adenosine kinase expression shows biphasic changes under pathological conditions (Boison, 2016). In the acute phase, there is an acute surge in adenosine associated with transient downregulation of adenosine kinase within the first few hours following an insult. In the chronic phase, adenosine kinase is upregulated as astrocytes and microglia become activated, leading to adenosine deficiency. Numerous studies have reported the upregulation of adenosine kinase in astrocytes in epileptic animal models and human temporal lobe epilepsy patients (Gouder et al., 2004; Boison, 2012). For example, Fedele et al. (2005) reported that astrogliosis is accompanied by the overexpression of adenosine kinase in a kainic acid (KA)–induced mouse model. Similarly, Aronica et al. (2011) reported that overexpressed adenosine kinase in an electricity-induced epilepsy model colocalized with glial fibrillary acidic protein, suggesting that reactive astrocytes may promote epilepsy development by upregulating adenosine kinase.

Astrocytes can also release various glial-related neurotransmitters, including glutamate, GABA, adenosine triphosphate, and D-serine, which mediate neuronal excitation or inhibition (Mahmoud et al., 2019). For example, astrocytes can release glutamate via the calcium-activated anion channel Bestrophin-1. Under physiological conditions, Bestrophin-1 is expressed primarily in specific microdomains of hippocampal astrocytes neighboring glutamatergic synapses. Elevated astrocytic calcium levels lead to the opening of Bestrophin-1 channels, resulting in the release of glutamate and the modulation of synaptic activity (Oh and Lee, 2017). Similarly, increased activity of the glutamate transporter can trigger GABA release via the glutamate/GABA exchange mechanism (Héja et al., 2012). Importantly, D-serine released by astrocytes serves as an endogenous coagonist of N-methyl-D-aspartate receptors, regulating the strength of excitatory synapses (Shleper et al., 2005; Abreu et al., 2023).

Disruption of neuronal microenvironment homeostasis

The neuronal microenvironment refers to the immediate surroundings and conditions in which neurons exist and function. It is dynamic and strongly influenced by glial cells, contributing significantly to the progression of epilepsy. Astrocytes also play crucial roles in maintaining water and potassium homeostasis through key proteins such as aquaporin-4 (AQP4), inwardly rectifying potassium channels 4.1, and gap junctions. In the CNS, aquaporins (particularly AQP4) are the primary regulators of water homeostasis. They are abundantly expressed in astrocytic endfeet, which cover the brain's blood vascular endothelial cells. Astrocyte-specific *Aqp4* knockout mice exhibit reduced brain water uptake in response to hypoosmotic stress and delayed postnatal resorption of brain water, providing compelling evidence for the involvement of astrocytes in the CNS water balance via AQP4 (Haj-Yasein et al., 2011). Additionally, ion concentrations in brain tissue influence neuronal activity. During an action potential, the extracellular potassium concentration can increase fourfold, with most potassium ions subsequently reimported by neurons via the Na^+/K^+-ATPase pump (Patel et al., 2019). Astrocytes contribute to the removal of excess potassium by expressing inwardly rectifying potassium channels 4.1, which colocalize with AQP4 on astrocytic endfeet (Kinboshi et al., 2020). Gap junctions facilitate the spatial buffering of potassium within the gap junction-coupled astrocytic network (Coulter and Steinhäuser, 2015; Dossi et al., 2024). Excessive local K^+ concentrations can lead to seizures, and the downregulation of Kir in glial cells may contribute to the onset of epilepsy (Coulter and Steinhäuser, 2015; Du et al., 2018). The diuretics furosemide and bumetanide exert antiepileptic effects by blocking the cotransporter of Na^+-K^+-2 Cl^- in glial cells, thereby reducing cell volume (Kaila and Löscher, 2022). Neuronal excitability is closely linked to water and the extracellular space. An increase in the extracellular space results in a reduction in neuronal and glial cell volume, leading to decreased cell excitability, and *vice versa*. Hence, water imbalance can trigger seizures. A significant decrease in the expression of AQP4 on astrocyte foot processes is observed in epileptic tissues (Lee et al., 2012), which leads to impaired water molecule transport and causes astrocyte swelling, extracellular space contraction, and increased excitability (Cha et al., 2023).

Astrocytes also play an important role in the energy supply or energy metabolism of neurons via the astrocyte–neuron lactate shuttle (Beard et al., 2022). Specifically, astrocytes take up glucose from the bloodstream via glucose transporter 1 and convert it to lactate using LDH 5. This lactate is then released into the extracellular space and transported into neurons (Jha and Morrison, 2018). Lactate serves as an alternative fuel source for neurons after conversion to pyruvate by LDH 1, contributing to oxidative phosphorylation, or acts as a modulator of neuronal functions, including excitability, plasticity, and memory (Magistretti and Allaman, 2018). In addition to lactate production through LDH5 and glycolysis, astrocytes can also generate lactate by mobilizing glycogen reserves (Hirase et al., 2019). Overall, the astrocyte–neuron energy metabolism interaction relies mainly on the astrocyte–neuron lactate shuttle pathway, particularly during periods of high neuronal activity. With respect to energy metabolism in epilepsy, the enhancement of the astrocyte–neuron lactate shuttle is widely accepted as a response of astrocyte–neuron metabolic coupling to the increased energy demand in neurons, especially during seizure conditions (Vezzani et al., 2022). The overexpression of LDH, the critical enzyme in the astrocyte–neuron lactate shuttle that catalyzes the conversion of lactate into pyruvate by neurons, which is subsequently used as an energy source through the tricarboxylic acid cycle, has been reported in reactive astrocytes in animal and human studies (Sada et al., 2020; Yilmaz and Tekten, 2021). Elevated astrocyte-derived lactate becomes an essential energy source for hyperactive neurons (Boison and Steinhäuser, 2018; **Figure 3**). In addition, excessive lactate acts as a signaling molecule, increasing neuronal excitability by potentiating N-methyl-D-aspartate receptor-mediated currents and the resulting increase in intracellular calcium (Yang et al., 2014). These findings indicate that reactive astrocytes establish a harmful cycle by increasing the expression of LDH and its ability to provide more lactate to neurons.

Lipid metabolism is crucial to normal astrocytic function and is therefore a key intermediate in neuron–astrocyte crosstalk (Barnes–Vélez et al., 2023). Astrocytes play a crucial role in neuronal lipid metabolism, where lipids and their intermediates participate in signal transduction and synaptic transmission, exerting essential functions in brain structure, function, and various physiological and pathological processes (Falomir-Lockhart et al., 2019). However, both human and mouse data demonstrate that excessive lipid accumulation in the brain is a significant pathological feature of epilepsy (Ahamad and Ge, 2021). Under pathological conditions, upregulated apolipoprotein E, which is predominantly expressed by astrocytes, mediates the transfer of toxic fatty acids produced by hyperactive neurons into astrocytes themselves, resulting in lipid droplet accumulation (Ioannou et al., 2019; **Figure 3**). Excessive lipids are believed to be degraded through mitochondrial β-oxidation, which is dependent on the strong antioxidant capacity of astrocytes (Su et al., 2024). However, this capacity is impaired in epilepsy, and neurons are exposed to toxic fatty acids.

Exacerbation of neuroinflammation

Accumulating evidence shows that neuroinflammation is a pathological hallmark of epileptic foci and is characterized by the activation of glial cells, the infiltration of peripheral immune cells, and the concomitant production of inflammatory mediators (Pracucci et al., 2021; **Figure 3**). The interaction between reactive astrocytes and microglia plays a pivotal role in the pathophysiology of epilepsy, which is characterized by a dynamic and complex relationship that exacerbates neuroinflammation and neuronal excitability. Upon activation due to seizures or brain injury, reactive astrocytes undergo morphological changes and release

proinflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor-α, and IL-6. These cytokines activate microglia through receptors such as Toll-like receptors and purinergic receptors, initiating inflammatory cascades that lead to further release of cytokines, including additional IL-1β and chemokines (Devinsky et al., 2013). This interaction establishes a neuroinflammatory feedback loop, where microglial activation promotes the release of cytokines such as IL-1α, tumor necrosis factor-α, and C1q, which contribute to the further activation of astrocytes (Liddelow et al., 2017). Specific signaling pathways, such as the nuclear factor-kappa light chain enhancer of B cells (NF-κB) and mitogen-activated protein kinase pathways, are central to this interaction. NF-κB is activated by proinflammatory cytokines and contributes to the sustained inflammatory response by promoting the expression of additional inflammatory mediators in both astrocytes and microglia. Similarly, the mitogen-activated protein kinase pathway, involving extracellular signal-regulated kinase, c-Jun NH2-terminal kinase, and p38 mitogen-activated protein kinase, regulates the activation and function of both cell types, increasing the production of cytokines and contributing to neuronal excitotoxicity.

Under homeostatic conditions, almost no types of lymphocytes can be found in the brain parenchyma, neither in humans nor in mice (Prinz and Priller, 2017; Papazian et al., 2024). While astrocytes and endothelial cells form a structural barrier, perivascular macrophages located on the abluminal side of the vascular tube form an immune barrier (Daneman and Prat, 2015). When CNS insult occurs, astrocytes produce IL-27 to limit proliferation and cytokine release in T cells (Yang et al., 2012); additionally, astrocytes modulate the activity of NK cells and B cells via IL-15 (Li et al., 2017) and chemokine ligand 12 (Krumbholz et al., 2006), respectively. In response to inflammatory signals, the phenotypic transformation of astrocytes is promoted by cytokines from infiltrating peripheral immune cells, such as interferon-γ from NK cells and IL-17 from T cells (Lee et al., 2023).

Participation in the formation of abnormal neural circuits

Synapses are the fundamental units of neural circuits. Astrocytes play a crucial role in the formation of synapses (Shan et al., 2021). They produce and release various synaptogenic factors, such as thrombospondins, which are crucial for initiating the formation of synapses (Mazur et al., 2021). Once synapses are formed, astrocytes adjust their coverage of synaptic elements in response to neuronal activity, promoting the longevity and efficacy of synaptic transmission (Noriega-Prieto and Araque, 2021). Astrocytes actively release gliotransmitters such as glutamate, D-serine, and adenosine triphosphate, which directly interact with neuronal receptors to modulate synaptic strength and plasticity (Sancho et al., 2021). These substances can enhance or suppress synaptic activity, contributing to both long-term potentiation and long-term depression, crucial mechanisms underlying learning and memory. Additionally, astrocytes are actively involved in pruning unnecessary synapses during development and in the adult brain to optimize neural networks (Park and Chung, 2023). They engulf and digest synaptic components, which is essential for eliminating excess or weak synaptic connections that are not functionally necessary, thereby refining neural connectivity and enhancing brain efficiency. To remove dysfunctional synapses, astrocytes can release various molecules that signal the need for synapse removal. For example, they produce and secrete complement proteins, which tag synapses for elimination (Irala et al., 2024). This action is part of a larger regulatory mechanism where astrocytes help identify and remove synapses that are less active or maladaptive, supporting synaptic plasticity and cognitive functions.

The formation of abnormal neural circuits has been demonstrated to be involved in the progression of epilepsy. During the development of epilepsy, two important forms of abnormal neural circuit formation occur. The first is the remodeling of existing circuits. The most typical example is hippocampal mossy fiber sprouting, in which the axons of granule cells in the dentate gyrus grow new projections and form aberrant synaptic connections with the dendrites of neighboring granule cells (Freiman et al., 2021). The second form involves the creation of new excitatory circuits, in which newly born granule cells in the dentate gyrus play a significant role (Chen et al., 2023a). During these two processes, the Janus kinase-signal transducer and activator of transcription protein-3 pathway plays an instrumental role. Reactive astrocytes are characterized by the activation of the Janus kinase-signal transducer and activator of transcription protein-3 pathway, which regulates perineuronal astrocytic process formation and the re-expression of thrombospondin-1 (**Figure 3**), a synaptogenic molecule (Nicolas et al., 2012; Tyzack et al., 2014). Specifically, reactive astrocytes participate in three main ways: extracellular matrix remodeling, inflammatory responses, and dysfunctions in glial transmission. In epilepsy and other neurological disorders, reactive astrocytes overexpress various extracellular matrix components, such as proteoglycans, tenascins, and chondroitin sulfate proteoglycans, which alter the structural and biochemical landscape of the extracellular matrix (Woo and Sontheimer, 2023). This leads to the disruption of normal synaptic connections and promotes the formation of aberrant neural networks. On the other hand, activated astrocytes release proinflammatory cytokines, contributing to chronic inflammation. This inflammatory environment can impair synaptic integrity, leading to abnormal neural connections and circuit formation. Furthermore, astrocytes release gliotransmitters such as adenosine triphosphate, glutamate, and D-serine, which modulate synaptic activity. In epilepsy, dysregulated release of these substances can exacerbate neuronal excitability and promote the formation of hyperactive neural circuits.

Targeting Astrocytes for Epilepsy Therapy

Given the crucial role of astrocytes in epileptogenesis, targeting reactive astrocytes as a therapeutic approach holds great promise in modifying or even curing epilepsy. In the following sections, we discuss potential therapeutic targets in astrocytes (**Table 1** and **Figure 4**), which may be helpful in restoring the balance of excitation-inhibition, as well as metabolic homeostasis in the neuronal microenvironment in epilepsy.

Restoring the excitation–inhibition balance of neurons

Glutamate transporters

Epilepsy is characterized by hyperexcitability of the CNS, which is attributed to excessive glutamate release from highly synchronized neurons into the synaptic space. Under physiological conditions, astrocytes are responsible for clearing extracellular glutamate primarily through excitatory amino acid transporter 2 (Peterson and Binder, 2020). The rapid clearance of excess synaptic glutamate by astrocytes terminates its action, regulates excitatory neurotransmission, and prevents inadvertent activation of extrasynaptic N-methyl-D-aspartate receptors linked to proapoptotic pathways (Patel et al., 2019). However, increased levels of extracellular glutamate have been detected in both animal and human epileptic tissues, which is attributed to decreased expression or malfunction of glutamate transporters. Thus, glutamate transporters are attractive targets for epilepsy modification studies (Celli and Fornai, 2021; Peterson et al., 2021; **Figure 5**). Gao et al. (2017) reported that saikosaponin A increased excitatory amino acid transporter 1 expression and improved the capacity of astrocytes to reuptake glutamate by inhibiting microRNA-155 expression in an intraperitoneal pentylenetetrazol-induced rat model. Ceftriaxone, a beta-lactam antibiotic, has been reported to increase glial GLT-1 transcription through the nuclear factor-kappa B signaling pathway (Lee et al., 2008). Ramandi et al. (2021) administered ceftriaxone to rat models of temporal lobe epilepsy induced by intraperitoneal lithium–pilocarpine injection and observed pharmacological upregulation of GLT-1 expression. Additionally, in the acute phase, ceftriaxone can reduce glutamate levels and increase the activity of glutamine synthetase. Moreover, long-term administration of ceftriaxone also rescued impaired learning and memory abilities during epileptogenesis. Furthermore, in an intrahippocampal KA-induced mouse model of epilepsy, a specific adeno-associated virus vector targeted to astrocytes was developed to promote GLT-1 transcription under the glial fibrillary acidic protein promoter (Peterson et al., 2021). This study demonstrated that GLT-1 upregulation in astrocytes could reduce seizure frequency.

In addition to increasing the expression of glutamate transporters, other studies have sought to protect these transporters from degradation (Song et al., 2020; Yamaguchi et al., 2020). Heat shock protein 90β, known for its role in protein folding, protein degradation, and signal transduction, plays a significant role in the stress response (Whitesell and Lindquist, 2005). Since a previous reports has indicated increased heat shock protein 90β expression in neurons and astrocytes in the hippocampal area in temporal lobe epilepsy models (Kandratavicius et al., 2014), subsequent studies have investigated the relationship between heat shock protein 90β and GLT-1 (Sha et al., 2020; Liang et al., 2024). According to a study by Sha et al. (2017), heat

Table 1 | **Summary of recent studies investigating astrocyte-targeted therapies for epilepsy**

Therapeutic strategies	Therapeutic targets	Epilepsy models	Mechanisms	Outcomes	References
Restoring the excitation/inhibition balance	NF-κB pathway	Pilocarpine/intraperitoneally	Pharmacological upregulation of GLT-1	Decreased glutamate level	Ramandi et al., 2021
	Astrocytic genome	KA/intrahippocampally	Astrocyte-specific upregulation of GLT-1	Decreased glutamate level	Peterson et al., 2021
	AP-1/miR-155/GLAST	pentylenetetrazol/intraperitoneally	Upregulation of GLAST	Decreased glutamate level	Gao et al., 2017
	heat-shock protein 90β	KA/intrahippocampally	Inhibiting the degradation of GLT-1	Decreased glutamate level	Sha et al., 2017
	Excitatory amino acid transporter 2	Pilocarpine/pentylenetetrazol/ intraperitoneally	Allosteric modulation of excitatory amino acid transporter 2	Decreased glutamate level	Fachim et al., 2011; Fachim et al., 2015
	Cystine/glutamate antiporter	Beta-1 integrin knockout model	Cystine/glutamate antiporter inhibitor	Decreased glutamate level	Alcoreza et al., 2019
	Astrocyte-specific leptin receptor	Pilocarpine/intraperitoneally	Antioxidant	Protecting astrocytes from glutamate toxicity	Jayaram et al., 2013
	Estradiol receptor	Pilocarpine/intraperitoneally	Upregulation of GLT-1 and glutamine synthetase	Decreased glutamate level	Sarfi et al., 2017
	GABA transporter, GAT-2/3	WAG/Rij rats a genetic model of absence epilepsy;	GABA precursor	Increased GABA level	Kovács et al., 2022
	Astrocyte genome	KA-Best1 KO-TLE/ intrahippocampally	Astrocyte-specific overexpression of Best 1	Enhanced GABA level	Pandit et al., 2020
	P2Y1 receptor	KA/intracortically	P2Y1 receptors inhibitor	Decreased glutamate level	Nikolic et al., 2018
Rebuilding metabolic homeostasis of microenvironment	Kir channel	Hippocampal slice/perfused with aCSF containing 4-AP	Enhancing the function of Kir	Buffered potassium	Barbaro et al., 2004
	Astrocyte-neuron lactate shuttle	KA/intrahippocampally	LDH inhibitor	Decreased neuronal excitability	Sada et al., 2015
	Lipid metabolism	KA/intrahippocampally	APOE mediated lipid accumulation in astrocytes	Increased neuronal excitation	Chen et al., 2023b
	adenosine kinase	KA/intrahippocampally	Nonselective adenosine kinase inhibitor	Decreased adenosine kinase level	Sandau et al., 2019
	Astrocyte genome	Spontaneously epileptic mice that overexpress adenosine kinase	Astrocyte-specific downregulation of adenosine kinase	Decreased adenosine kinase level	Theofilas et al., 2011
	Astrocyte genome	KA/intrahippocampally	Astrocyte-specific downregulation of adenosine kinase	Decreased adenosine kinase level	Young et al., 2014
	Gap junctions	4-AP/intracortically	Gap junction blocker	Buffered potassium level	Volnova et al., 2022
	Na^+-K^+-ATPase	KA/intracortically	Cation channel	Buffered potassium level	Zhao et al., 2022
Modulating CNS inflammation and immunity	Angiotensin receptor 1	Pilocarpine/intraperitoneally	Angiotensin receptor blocker	Preventing astrocyte activation	Hong et al., 2019
	TRPV 4	4-AP/intraperitoneally	TRPV 4 inhibitor	Preventing astrocyte activation	Zeng et al., 2022
	Astrocytic autophagy	Pentylenetetrazol/intraperitoneally	COX inhibitor	Preventing astrocyte activation	Peng et al., 2019
	Gasdermin D	KA/intrahippocampally	Gasdermin D inhibitor	Preventing astrocyte activation	Xia et al., 2021
	Astrocytic Nrf 2-NF-κB signaling pathway	Pilocarpine/intraperitoneally	Inhibit Nrf 2-NF-κB signaling pathway	Preventing astrocyte activation	Xian et al., 2019
	p27-ERK 1/2 pathway	Pilocarpine/intraperitoneally	CRM1 inhibitor	Preventing astrocyte activation	Kim and Kang, 2018
	TGF-β pathway	TGF-β1/IL-1β stimulated primary astrocytes	Negative regulator of proepileptogenic factors	Preventing astrocyte activation	Korotkov et al., 2020
	Astrocyte genome	IL-1β-stimulated human fetal astrocytes	Anti-inflammation	Preventing astrocyte activation	van Scheppingen et al., 2018
	mTOR pathway	KA/intraperitoneally	mTOR inhibitor	Preventing astrocyte activation	Guo et al., 2017
	Adenosine kinase	$Adk^{-/-}$ ES cells	Inducing differentiation of $Adk^{-/-}$ astrocyte	Increasing adenosine level	Fedele et al., 2004
	Astrocyte genome	Pilocarpine/intraperitoneally	Converting reactive astrocytes into GABAergic neurons	Increasing GABAergic neurons	Zheng et al., 2022
Reconstructing the abnormal neural circuits	mTOR pathway	Pilocarpine/intraperitoneally	mTOR inhibitor	Inhibiting the mossy fiber sprouting	Hester et al., 2016
	Toll-like receptor 4	Pentylenetetrazol/intraperitoneally	Inhibiting Erk 1/2 pathway	Suppressing excitatory synaptogenesis	Shen et al., 2016
	Subiculum	Kindling-induced seizures	Inhibiting the projection between subiculum and ANT	Suppressing seizure propagation	Fei et al., 2022
	Adult-born dentate granule cells	KA/intrahippocampally	Inhibiting local aberrant excitatory circuits	Reducing seizure predisposition	Chen et al., 2023a

This table summarizes therapeutic targets on astrocytes on the basis of preclinical studies, which can be categorized into four aspects: restoring the excitation–inhibition balance, reestablishing metabolic homeostasis of the neuronal microenvironment, modulating CNS inflammation and immunity, and reconstructing abnormal neural circuits. aCSF: Artificial cerebrospinal fluid; ANT: anterior nucleus of the thalamus; APOE: apolipoprotein E; Best 1: Bestrophin 1; COX: cyclooxygenase; CRM 1: chromosome region maintenance 1; ES: embryonic stem; Erk: extracellularly regulated protein kinases; 4-AP: 4-aminopyridine; GABA: gamma-aminobutyric acid; GAT-2/3: gamma aminobutyric acid transporter 2/3; GLT-1: glutamine transporter 1; GLAST: glutamate-aspartate transporter; IL: interleukin; KA: kainic acid; KO: gene knockout; LDH: lactate dehydrogenase; MDR: multidrug resistance; miR: microRNA; mTOR: mammalian target of rapamycin; NeuroD1: neurogenic differentiation 1; Nrf2: nuclear factor erythroid 2-related factor 2; NF-κB: nuclear factor-kappa light chain enhancer of B cells; PPAR-γ: peroxisome proliferator-activated receptor gamma; shRNA: short hairpin RNA; siRNA: small interfering RNA; TGF-β: transforming growth factor-β; TLE: temporal lobe epilepsy; TRPV 4: transient receptor potential vanilloid 4; WAG/Rij: Wistar Albino Glaxo Rijswijk.

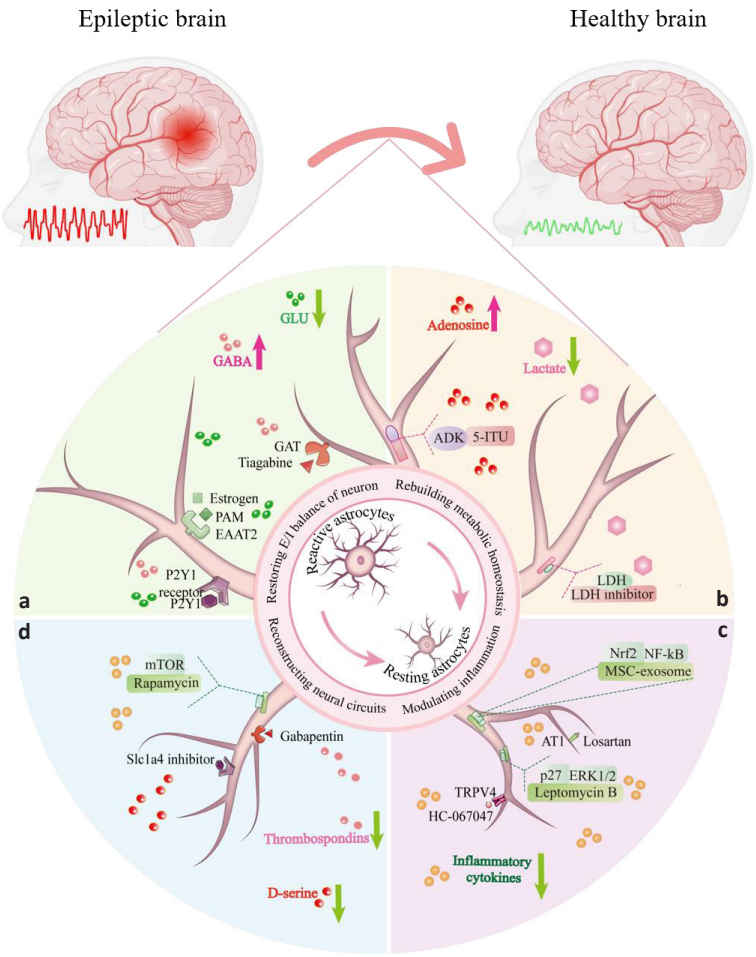

Figure 4 | **Reactive astrocytes represent viable targets for epilepsy treatment through several mechanisms.**
(a) Restoring the excitation–inhibition balance by decreasing glutamate or increasing GABA in the synaptic cleft. (b) Reestablishing metabolic homeostasis by inhibiting the astrocyte neuron lactate shuttle pathway, increasing adenosine, downregulating AQP4 expression and upregulating the expression of inwardly rectifying potassium channels 4.1. (c) Modulating immune and inflammatory homeostasis to prevent astrocyte activation. (d) Reconstructing neural circuits by inhibiting mossy fiber sprouting and newly formed excitatory circuits by regulating the release of thrombospondin 1, D-serine and Sparcl 1 (red arrow represents upregulation; green arrow represents downregulation). AQP 4: Aquaporin 4; GLU: glutamate; GABA: gamma-aminobutyric acid; TSP: thrombospondin.

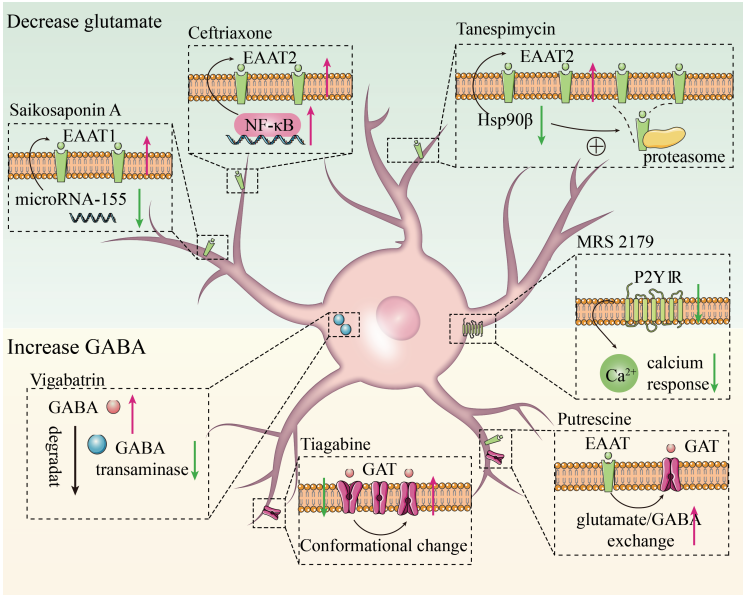

Figure 5 | **Restoring the excitation–inhibition balance by targeting astrocytes.**
Neuronal hyperexcitability can be mitigated by decreasing glutamate and increasing GABA (red arrows represent upregulation, and green arrows represent downregulation). EAAT: Excitatory amino acid transporter; GABA: gamma-aminobutyric acid; GAT: GABA transporter; GLU: glutamate; Hsp90β: heat-shock protein 90 kDa; P2Y1R: purinergic G protein-coupled receptor P2Y1.

shock protein 90β facilitates the recruitment of GLT-1 to the 20S proteasome, promoting its degradation (**Figure 5**). By administering tanespimycin, a heat shock protein 90β inhibitor, GLT-1 degradation is prevented by disrupting the association between heat shock protein 90β and GLT-1. In a mouse temporal lobe epilepsy model induced by intrahippocampal injection of KA, the administration of tanespimycin increased the expression of GLT-1, which in turn suppressed spontaneous recurrent seizures and reduced astrogliosis. These findings suggest that inhibiting heat shock protein 90β in reactive astrocytes may be an alternative therapeutic strategy for epilepsy.

In addition to regulating the expression of GLT-1 through pharmacological or genetic methods, another promising approach involves enhancing the ability of existing GLT-1 to increase glutamate reuptake. Allosteric modulators are substances capable of binding to an allosteric site, resulting in a conformational change in the primary orthosteric binding site of the biological target. This modification can affect the binding of natural ligands to the orthostatic site of enzymes or receptor proteins (Abdel-Magid, 2015). Among them, positive allosteric modulators have gained considerable attention in the field of epilepsy because they increase the binding affinity between the target and its ligand. Positive allosteric modulators of transporters directly and selectively bind to the transporter itself on the membrane, interacting with the interface between the transport and scaffolding domains. This alters the equilibrium of different transporter conformations and leads to increased activity (Green et al., 2021). For example, Parawixin 10, a nonselective positive allosteric modulator of GLT-1, has been shown to protect neurons from excitotoxicity and reduce seizure susceptibility in rats that receive intrahippocampal injections of N-methyl-D-aspartate (Fachim et al., 2011, 2015). These findings provide a novel therapeutic strategy worth considering.

Cystine/glutamate antiporters

While the cystine/glutamate antiporter, also called system xc^-, plays a role in redox homeostasis, under pathological conditions, it has been reported to exacerbate glutamate excitotoxicity. The upregulation of the cystine/glutamate antiporter could be mitigated by sulfasalazine, a nonselective inhibitor of the cystine/glutamate antiporter that is FDA-approved for treating inflammatory bowel disease. Alcoreza et al. (2019) conducted an *in vitro* study to assess the effect of sulfasalazine on pharmacologically induced network excitability. Using cortical mouse brain slices, they reported that a decrease in sulfasalazine evoked excitatory postsynaptic currents induced by bicuculline and magnesium-free solutions. Another study by Alcoreza et al. (2022) demonstrated that sulfasalazine can reduce both seizures and epileptic discharges in a β1-integrin knockout mouse model of astrogliosis-mediated epilepsy. Whole-cell recordings revealed hyperpolarized neurons in cystine/glutamate antiporter and β1-integrin double-knockout mice. The upregulation of the cystine/glutamate antiporter and the antiepileptic effect of sulfasalazine have also been confirmed in an intraperitoneal pilocarpine-induced epilepsy mouse model (Leclercq et al., 2019).

Concerns arise regarding excessive oxidative stress when the cystine/glutamate antiporter is inhibited, as it is a crucial component of the antioxidant system. However, De Bundel et al. (2011) proposed that the loss of the cystine/glutamate antiporter did not induce oxidative stress but rather decreased extracellular glutamate levels and seizure susceptibility. They reported that oxidative stress–related markers did not change upon cystine/glutamate antiporter deletion, suggesting the presence of compensatory mechanisms for cystine import loss via the cystine/glutamate antiporter. Notably, stimulation of the cystine/glutamate antiporter with N-acetylcysteine, a cysteine precursor, significantly increased the level of extracellular glutamate in the hippocampus. The precise role of the cystine/glutamate antiporter in glutathione synthesis and redox balance remains to be elucidated. According to these studies, the regulation of the cystine/glutamate antiporter on astrocytes provides a promising target for epilepsy therapy in future studies.

Leptin receptor

Leptin is a hormone that is mainly secreted by adipose tissue and then transported into the CNS across the BBB; it is also endogenously synthesized by neurons. Leptin plays a crucial role in mediating neuronal survival signals by alleviating mitochondrial oxidative stress via the Janus tyrosine kinase 2/signal transducer and activators of the transcription pathway (Signore et al., 2008; Shan et al., 2023). In the CNS, several studies have reported a strong association between epilepsy and the upregulation of leptin receptors in astrocytes (Liu et al., 2023; Sun et al., 2024). Obeid et al. (2010) demonstrated that intraperitoneal leptin injections reduce the degree of cellular injury associated with intraperitoneal KA-induced status epilepticus in rats. However, the injection of leptin did not prevent long-term recurrent spontaneous seizures or behavioral deficits. Jayaram et al. (2013) conducted *in vitro* and *in vivo* studies to explore the relationship between the leptin system and glutamate-induced cytotoxicity. They reported that leptin receptors were overexpressed in the seizure focus of pilocarpine-induced models, as well as in cultured astrocytes pretreated with glutamate. Importantly, both *in vivo* and *in vitro* trials demonstrated that the administration of leptin alleviated the neurotoxic effects of excess extracellular glutamate. The protective role of astrocytic leptin signaling was further confirmed by increased mortality in mice with astrocyte-specific leptin receptor knockout. Thus, leptin signaling in astrocytes plays a protective role against seizures, which is partially mediated by the attenuation of glutamate toxicity. Although the exact role of leptin in epileptogenesis has yet to be elucidated, astrocytic leptin signaling represents an attractive target for epilepsy treatment.

Gamma-aminobutyric acid receptors and transaminases

GABA is the primary inhibitory neurotransmitter in the CNS. After being released into the synaptic space by GABAergic neurons, GABA binds to receptors on the postsynaptic membrane and is taken up by GABA transporters into glial cells, where it is then metabolized by GABA transaminase (Treiman, 2001). Strategies that enhance GABA receptor function or increase synaptic GABA levels by inhibiting GABA metabolism have shown promise in the treatment of epilepsy. For example, many antiseizure medications, such as benzodiazepines and barbiturates, have been developed to directly target GABA receptors on neurons. Recent studies have explored nonneuronal cell modulation of GABA metabolism (Andersen et al., 2020; Zhuravleva and Zhuravlev, 2023). For example, tiagabine, a clinically used ASM, locks GABA transporter 1 (a GABA transporter subtype) in an inward-open conformation by blocking the intracellular gate of the GABA release pathway, thereby suppressing neurotransmitter uptake (Motiwala et al., 2022; **Figure 5**). Another ASM, vigabatrin, irreversibly inhibits GABA transaminase, leading to the inhibition of GABA degradation (Treiman, 2001). Interestingly, GABAergic inhibition can be enhanced through the release of glutamate via a glutamate/GABA exchange mechanism (Héja et al., 2012). Briefly, glutamate uptake by astrocytes increases the intracellular sodium concentration, disrupting the resting electrochemical potential. Since the sodium gradient also drives GABA transport, increased intracellular sodium may facilitate the reverse release of GABA by reversing GABA transporters. In a recent study, Kovács et al. (2022) reported that putrescine, a GABA precursor, intensified the glutamate/GABA exchange mechanism and promoted early termination of seizures in a WAG/Rij rat model of absence epilepsy (**Figure 5**). They further confirmed that putrescine specifically reduced the frequency of excitatory synaptic potentials, suggesting its specific action at excitatory synapses. Future *in vivo* studies examining putrescine in temporal lobe epilepsy animal models are warranted.

Bestrophin 1, known for its role as an anion channel and regulator of intracellular Ca^{2+} signaling, has been extensively studied in retinal diseases (Johnson et al., 2017). In the CNS, however, it is reported to mediate tonic inhibition via GABA release from astrocytes. Pandit et al. (2010) reported elevated electroshock-induced seizure activity in bestrophin 1 knockout mice intracerebroventricularly after KA injection, but astrocyte-specific overexpression of bestrophin 1 restored seizure susceptibility. Importantly, this effect did not result from alterations in GABA receptors or transporters.

Purinergic G protein-coupled receptor P2Y1

The purinergic G protein-coupled receptor P2Y1 ($P2Y_1R$) belongs to the family of G protein-coupled receptors and plays a crucial role in astrocyte physiology, participating in various cellular processes, such as development, metabolism, and cell–cell communication (Lohr, 2023). Previous studies have suggested that metabotropic purinergic G protein-coupled receptor P2Y1 activation contributes to epileptogenesis by inhibiting GABA transport (Jacob et al., 2014; Smith et al., 2024) and enhancing glutamate release (Zeng et al., 2008), which is dependent on increased astrocytic calcium signaling following neuronal firing. Therefore, the purinergic G protein-coupled receptor P2Y1 has emerged as a potential therapeutic target for epilepsy (Alves et al., 2019). Nikolic et al. (2018) reported that autocrine activation of the purinergic G protein-coupled receptor P2Y1 by astrocyte-derived adenosine triphosphate/adenosine diphosphate contributed to tumor necrosis factor α-induced calcium-dependent glutamate release by astrocytes, leading to increased CNS excitability (Nikolic et al., 2018). Notably, blocking these purinergic receptors with MRS 2179 completely prevented astrocyte-dependent increases in miniature excitatory postsynaptic current frequency induced by light stimulation or tumor necrosis factor α and abolished astrocytic calcium responses (**Figure 5**). Additionally, blockade of the purinergic G protein-coupled receptor P2Y1 has been shown to normalize network dysfunction and cognition by counteracting astrocytic hyperactivity in an Alzheimer's disease model (Delekate et al., 2014; Reichenbach et al., 2018).

Estrogen receptors

Estrogen, an endogenous hormone, is critical for normal brain metabolism, particularly in neuroendocrine circuits (Fuente-Martin et al., 2013). Early studies suggested that estrogen modulates neurotransmitter systems, including dopaminergic, serotonergic, and glutamatergic pathways (Chavez et al., 2010), which are key contributors to major psychiatric disorders. Additionally, estrogen has been shown to regulate synaptic plasticity through the induction of synaptogenesis (Kretz et al., 2004). Since estrogen signaling plays a significant role in the pathophysiology of CNS disorders, increasing research has aimed to explore its therapeutic effect. Previous *in vitro* studies have suggested that estrogen treatment increases glutamate uptake by increasing GLT-1 expression in astrocytes from patients with Alzheimer's disease (Tejeda-Bayron et al., 2021; Taxier et al., 2024). In an intraperitoneal pilocarpine-induced mouse model, Sarfi et al. (2017) reported that subcutaneous injection of estradiol could prolong seizure latency, reduce the rate of generalized clonic seizures, and increase the activity of glutamine synthetase and GLT-1 (**Figure 4**). Additionally, a high dose of estradiol can increase neuronal density. However, the effects of estrogen can be contradictory. Some recent studies have shown that estrogen can reduce inhibitory synaptic currents in entorhinal cortex neurons (Batallán Burrowes et al., 2024) and induce rapid excitations in neurons (Yu et al., 2024). The underlying mechanism of action of estrogen on the nervous system remains to be elucidated, but it appears that estrogen signaling exerts a regulatory effect on neurons that can be further investigated in future studies.

Rebuilding metabolic homeostasis

Lactate

The astrocyte–neuron lactate shuttle theory states that astrocytes accelerate their glucose uptake, glycolysis, and subsequent release of lactate into the extracellular space in response to intensified neuronal activity (Mason, 2017). LDH, an important component of the astrocyte–neuron lactate shuttle, has been experimentally shown to decrease lactate formation, which promotes epileptic seizures (Fei et al., 2020). Sada et al. (2015) reported that seizures and epileptiform activity were reduced by inhibiting

the metabolic pathway via LDH (**Figure 6**). They discovered that stiripentol, a clinically used antiepileptic drug, acts as an LDH inhibitor. Additionally, they identified a previously unknown LDH inhibitor through modification of the chemical structure of stiripentol. This antiepileptic effect was reversed when exogenous pyruvate, a downstream metabolite of LDH, was added. However, it should be noted that the benefit of inhibiting LDH may not solely result from suppressing the transformation of lactate to pyruvate. Recent studies emphasize that lactate should also be considered an important signaling molecule because of its contribution to several homeostatic processes in brain function (Colucci et al., 2023; Wang et al., 2023). These processes include the modulation of neuronal excitability, neuronal plasticity, and neuroprotection through interactions with different molecular effectors (Magistretti and Allaman, 2018).

Lipids

Dysregulated lipid metabolism has been reported in epilepsy. Chen et al. recently discovered a new subtype of reactive astrocytes called lipid-accumulated reactive astrocytes, characterized by elevated apolipoprotein E expression. Through single-nucleus RNA sequencing, the authors revealed abnormalities in lipid metabolism and apolipoprotein E upregulation in astrocytes from patients with temporal lobe epilepsy. Furthermore, they reported that lipid-accumulated reactive astrocytes promote neuronal discharges and exacerbate the ongoing pathology of epilepsy in intrahippocampal KA-induced temporal lobe epilepsy mouse models, possibly through the upregulation of astrocytic A2AR. This study provides the first evidence that apolipoprotein E is a crucial mediator of abnormal lipid metabolism in astrocytes and could serve as a potential target for epilepsy therapy (Chen et al., 2023b). It has been reported that the upregulation of apolipoprotein E-mediated GABAergic interneuron loss can lead to inhibitory network deficits, causing seizures in patients with Alzheimer's disease (Najm et al., 2019). However, this detrimental effect can be ameliorated with the small-molecule structure corrector PH 002, which corrects the pathogenic conformation of apolipoprotein E (Wang et al., 2018; **Figure 6**).

Water and ions

Downregulation of AQP4 expression has been demonstrated in the acute phase of a mouse epilepsy model induced by intrahippocampal injection of KA (Nicolas et al., 2012). However, AQP4 has also been reported to be overexpressed in samples from epilepsy patients or animal seizure models (Duan and Di, 2017; Salman et al., 2017). Lei et al. (2020) reported that AQP4 expression could be downregulated by inhibiting NR2A (using the NR2A antagonist PEAQX), a subunit of the N-methyl-D-aspartate receptor, leading to mitigated pentylenetetrazol-induced seizure severity (Lei et al., 2020). Hence, the expression of AQP4 in epilepsy appears to follow a biphasic pattern: a decrease in the acute phase, gradually returning to baseline, followed by an increase in the chronic phase (Hubbard et al., 2016). Nonetheless, targeting astrocytic AQP4 remains a potential therapeutic strategy for epilepsy.

During an epileptic seizure, hyperexcitable neurons release a substantial amount of potassium into the extracellular space. Astrocytes can help clear excessive potassium through Kir channels, particularly inwardly rectifying potassium channels 4.1, which are predominantly expressed by astrocytes in the brain (Seifert et al., 2009; Nwaobi et al., 2016). However, the downregulation of inwardly rectifying potassium channel 4.1 channels has been observed in hippocampal specimens obtained from patients with refractory temporal lobe epilepsy (Steinhäuser et al., 2012; Kitaura et al., 2018). Several drugs, such as guanosine (Benfenati et al., 2006; **Figure 6**), dexamethasone (Zhao et al., 2011), and minocycline (Zhang et al., 2011), have been reported to increase inwardly rectifying potassium channel 4.1 expression. Interestingly, furosemide, a clinically used drug to modulate blood pressure, reportedly enhances the function of astrocytic inward potassium channels (Barbaro et al., 2004). Gene therapy is also utilized to regulate potassium homeostasis. In a mouse model of focal cortical dysplasia in the frontal lobe, researchers used an engineered potassium channel transgene controlled by a human promoter that preferentially targets principal neurons. The gene was delivered via an adeno-associated viral vector 9. Injection of this vector into the dysplastic region significantly reduced seizure frequency. This approach highlights the promising translational potential of gene therapy for treating the epileptic manifestations of cortical malformations (Almacellas Barbanoj et al., 2024).

Gap junctions represent another important astrocytic structure involved in K^+ homeostasis. Once K^+ enters astrocytes through Kir channels, it is spatially buffered and redistributed through gap junctions into the syncytial network of gap junction-coupled astrocytes (Coulter and Steinhäuser, 2015). However, the modulation of gap junctions at both the expression and functional levels remains inconclusive (Patel et al., 2019). Both decreases and increases in gap junctions have been reported, and gap junction inhibitors have shown both anticonvulsant (Volnova et al., 2022) and proconvulsant (Voss et al., 2009) effects. Despite this uncertainty, the involvement of gap junctions in epileptogenesis suggests that they can serve as interesting targets for further investigation.

Adenosine

In a recent study, Sandau et al. (2019) investigated the antiepileptic effect of 5-iodotubercidin, a nonselective adenosine kinase inhibitor, in an intrahippocampal KA-induced mouse model. The treatment was initiated 3–8 days after injury and maintained during the latent phase of epileptogenesis. Their findings revealed that 5-iodotubercidin not only significantly reduced seizures by at least 80% in more than half of the mice but also suppressed granule cell dispersion and downregulated adenosine kinase. In addition to direct pharmacological inhibition of adenosine kinase, gene therapy is another popular research approach. Theofilas et al. (2011) expressed an antisense-oriented Adk-cDNA controlled by an astrocyte-specific GfaABC1D promoter, resulting in reduced adenosine kinase levels and fewer seizures in transgenic mice that overexpressed adenosine kinase. Young et al. (2014) successfully improved seizure control and protected neurons by decreasing adenosine kinase through microRNAs that target adenosine kinase in hippocampal astrocytes in epileptic mice induced by intrahippocampal KA injection, identifying ADK as a prime therapeutic target for gene therapy of temporal lobe epilepsy. In addition to targeting astrocytes, adenosine augmentation can be achieved by delivering exogenous adenosine or A1R agonists directly (Boison, 2016). Notably, high levels of adenosine may reduce DNA methylation, potentially contributing to the expression of specific genes associated with epileptogenesis through epigenetic mechanisms (Williams-Karnesky et al., 2013).

Modulating central nervous system inflammation and immunity

Angiotensin receptors, which are located primarily on neurons, mediate most of the physiological effects of brain angiotensin. However, the effects of angiotensin receptors on glial cells, especially astrocytes, have often been overlooked. Studies have demonstrated the presence of angiotensin receptor-like immunoreactivity for angiotensin receptor 1 and/or 2 in white matter astrocytes, suggesting a potentially significant role of astrocytes in the central renin–angiotensin system (Fogarty and Matute, 2001; Zuo et al., 2024). In an epilepsy rat model induced by intraperitoneal pilocarpine injection, Hong et al. (2019) reported that losartan, a clinically used blood pressure-regulating drug, reduced astrocyte activation, protected the BBB, and prevented the downregulation of AQP4 expression (**Figure 7**). However, this effect was not observed in the control group (Hong et al., 2019). Although losartan did not affect the severity of status epilepticus, it attenuated seizure spike activity and the development of spontaneous recurrent seizures during the chronic phase.

Transient receptor potential vanilloid 4 (TRPV4) is a member of the transient receptor potential channel family, which comprises nonselective cationic ion channels. TRPV4 is widely expressed throughout various systems in humans and is believed to mediate inflammatory responses by increasing the production of proinflammatory cytokines upon activation (Wang et al., 2019). In the CNS, TRPV4 is predominantly enriched in astrocytes (Dunn et al., 2013). Zeng et al. (2022) investigated the role of TRPV4 in a mouse model of acute epileptic seizure induced by 4-aminopyridine administration. Through bioinformatics screening, they identified Trpv4 as a seizure-associated gene and confirmed its upregulation in 4-aminopyridine-induced mice and epileptic patients. By intracerebroventricularly injecting a TRPV4 agonist, they reported an increase in 4-aminopyridine-induced seizure susceptibility and A1 phenotypic polarization of astrocytes, which could be significantly reversed by administering a TRPV4 inhibitor. Further exploration suggested that the transcription coregulator Yes-associated protein plays a crucial role in the downstream signaling pathway of TRPV4 activation. By providing evidence for the involvement of TRPV4 in promoting astrocyte activation and the production of proinflammatory cytokines in epilepsy, this study highlights TRPV4 as a potential therapeutic target for modulating inflammation in seizure treatment.

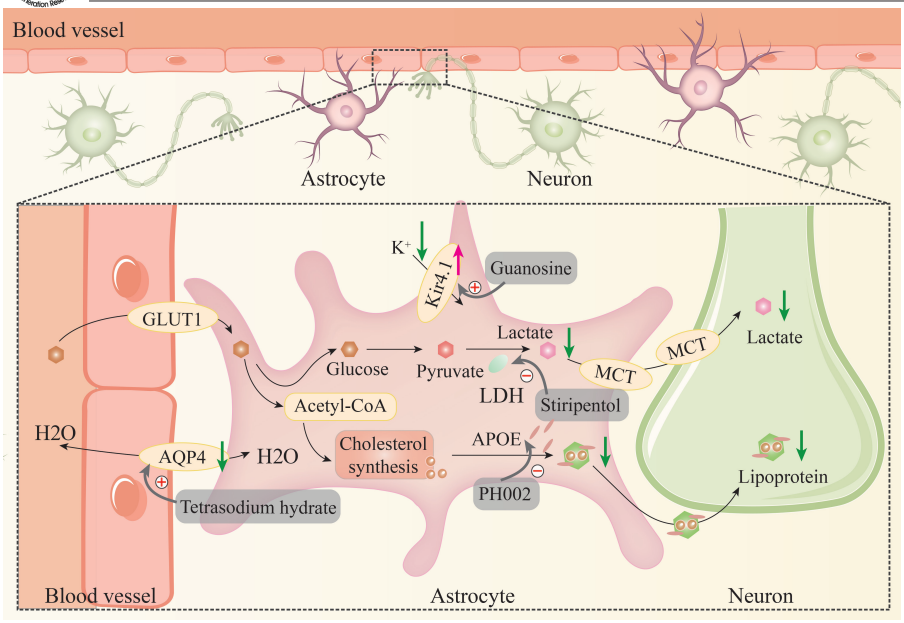

Figure 6 | **Targeting astrocytes to reestablish metabolic homeostasis in the neuronal microenvironment.**
Key approaches include suppressing lactate shuttle with LDH inhibitors, restoring water and ion balance with inwardly rectifying potassium channel 4.1 enhancers or gap junction inhibitors, and reshaping the metabolism of lipids with APOE modulators. Red arrows represent upregulation, green arrows represent downregulation, and gray squares represent drugs that were used in related studies. APOE: Apolipoprotein E; AQP 4: aquaporin 4; GLUT 1: glucose transporter 1; MCT: monocarboxylate transporter; Kir 4.1: inwardly rectifying potassium channel 4.1.

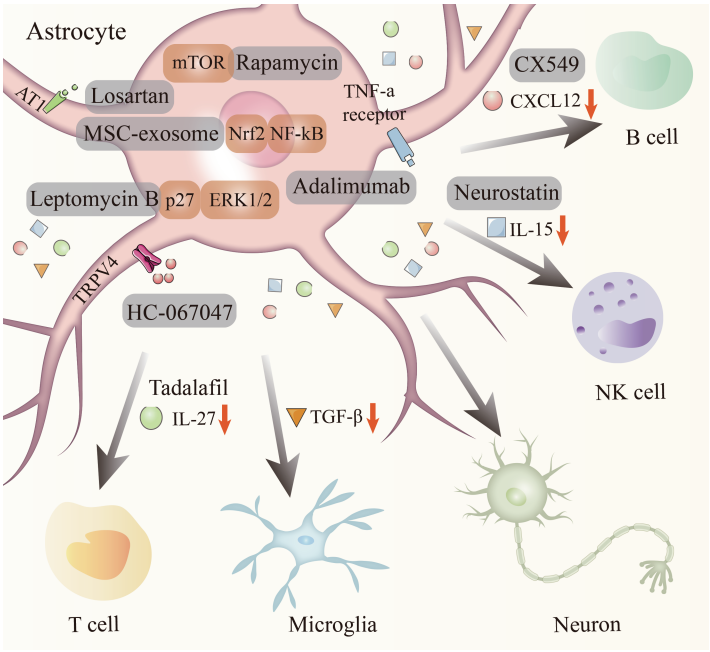

Figure 7 | **Modulating CNS inflammation and immunity by targeting astrocytes.**
The orange arrows represent downregulated drugs, and the gray squares represent drugs that were used in related studies. AT1: Angiotensin 1; CNS: central nervous system; CXCL: chemokine ligand; Erk: extracellularly regulated protein kinase; MSC: mesenchymal stem cell; Nrf 2: nuclear factor erythroid 2-related factor 2; IL: interleukin; TGF-β: transforming growth factor-β; TNF: tumor necrosis factor; TRPV 4: transient receptor potential vanilloid 4.

There are several other potential targets associated with proinflammatory astrocyte transformation and the release of inflammatory cytokines. Peng et al. (2019) reported that ibuprofen reduces astrocyte proliferation by increasing autophagy, thereby affecting the development of epilepsy in a rat model induced by intraperitoneal pentylenetetrazol administration. Inflammatory cytokines can stimulate the upregulation of Gasdermin D and caspase-1 proteins in cultured astrocytes, leading to astrocytic pyroptosis (Sun et al., 2019). Xia et al. (2021) reported that dimethyl fumarate, an inhibitor of N-terminal fragments of gasdermin D, alleviated the severity of seizures and astrocytic clasmatodendrosis, indicating that gasdermin D-mediated pyroptosis is involved in the mechanism of KA-induced seizures in a mouse model of epilepsy. Mesenchymal stem cell-derived exosomes are regarded as robust anti-inflammatory agents for treating various CNS diseases (Yang et al., 2017). Xian et al. (2019) demonstrated that mesenchymal stem cell-derived exosomes ameliorate lipopolysaccharide-induced astrocyte activation, likely through the NF-κB pathway. Kim and Kang (2018) initially reported that the export of nucleocytoplasmic cyclin-dependent kinase inhibitor 1B was necessary for extracellular signal-regulated kinase 1/2-mediated astroglial proliferation during reactive astrogliosis. Using leptomycin B to inhibit cyclin-dependent kinase inhibitor 1B export, they observed fewer activated astrocytes and improved seizure outcomes, suggesting that nuclear entrapment of cyclin-dependent kinase inhibitor 1B could be a potential therapeutic strategy for epilepsy (**Figure 7**). Additionally, Korotkov et al. (2020) reported increased expression of miR-132 in epileptogenic hippocampal tissue from both human patients and rats, particularly in glial cells. Transfection of microRNA-132 into human primary astrocytes reduced the expression of pro-epileptogenic cyclooxygenase-2, IL-1β, TGF-β2, monocyte chemoattractant protein-1, and matrix metallopeptidase 3.

Astrocytes have been shown to regulate the immune response in epilepsy by interacting with central and peripheral immune cells. In Rasmussen's encephalitis, antitumor necrosis factor alpha therapy (adalimumab) was reported to be effective (Lagarde et al., 2016), possibly by blocking the proinflammatory signal from microglia to astrocytes. CX 549 was demonstrated to inhibit the chemokine ligand 12/chemokine receptor 4 axis (Wu et al., 2017; **Figure 7**), which could reduce the activation of microglia and the recruitment of inflammatory B cells. Blockade of IL-15 activity with neurostatin inhibited microglial activation through the NF-κB, p38, and Erk 1/2 pathways (Gomez-Nicola et al., 2010), reducing cytokine and chemokine release as well as the infiltration of peripheral NK cells. In a sporadic Alzheimer's disease mouse model induced by intracerebroventricular injection of streptozotocin, tadalafil halted neuroinflammation by reducing IL-23 and IL-27 levels (Salem et al., 2021), which could limit proliferation and cytokine release in T cells (Yang et al., 2012).

Reconstructing abnormal neural circuits

Mossy fiber sprouting

Increased mammalian target of rapamycin activity has been implicated in the development of mossy fiber sprouting associated with temporal lobe epilepsy (Lasarge and Danzer, 2014). During the chronic phase of epileptogenesis in the intrahippocampal kainic acid model of temporal lobe epilepsy, phosphorylated ribosomal protein S6, a downstream target of the mammalian target rapamycin, is upregulated in hippocampal granule cells and reactive astrocytes. Notably, in the human sclerotic hippocampus, mammalian target of rapamycin signaling was predominantly observed in reactive astrocytes. Hester et al. demonstrated that systemic administration of the mammalian target of the rapamycin inhibitor rapamycin effectively inhibited S6 protein phosphorylation, reduced mossy fiber axon sprouting in granule cells, and decreased reactive astrocytosis (**Figure 8**; Hester et al., 2016). This intervention showed promising therapeutic potential by reducing both

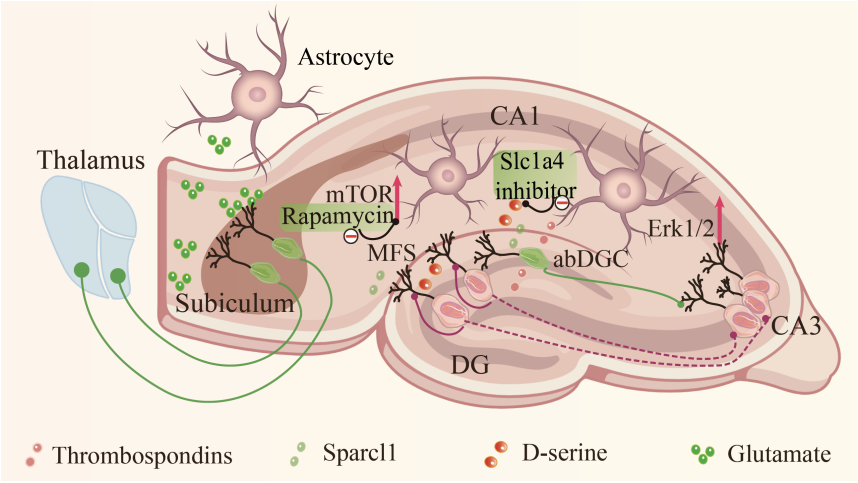

Figure 8 | Targeting astrocytes to reconstruct abnormal neural circuits for the treatment of epilepsy.
The activation of the mammalian target of rapamycin (mTOR) pathway, predominantly in astrocytes, promotes the progression of epilepsy via mossy fiber sprouting. Rapamycin, an mTOR inhibitor, has been demonstrated to improve epilepsy by suppressing the mTOR pathway and subsequent mossy fiber sprouting. Inhibiting extracellular signal-regulated kinases 1/2 in astrocytes can restore enhanced seizure sensitivity by suppressing newly formed excitatory synapses (red arrows represent upregulation, and yellow squares represent drugs that were used in related studies). abDGC: Adult-born dentate granule cells; DG: dentate gyrus; Erk: extracellular signal-regulated kinases; MFS: mossy fiber sprouting; mTOR: the mammalian target of rapamycin; Slcla 4: an amino acid transporter related to D-serine.

seizure frequency and severity in patients with pilocarpine-induced status epilepticus. Several studies have also demonstrated the effectiveness of targeting the anti-mammalian target of the rapamycin pathway in epilepsy treatment (Zeng et al., 2009; Hester and Danzer, 2013).

Newly formed aberrant excitatory circuits

Accumulating evidence has demonstrated that local aberrant excitatory circuits formed by adult-born hippocampal granule cells during a critical period of epileptogenic insult maintain seizure duration (Chen et al., 2023a). In this process, astrocytes play a crucial role in shaping a predisposition to seizure generation by controlling the generation and integration of excitatory synapses, which may serve as potential targets for antiepileptogenesis. Sultan et al. (2015) reported that the astrocytic release of D-serine locally controls the synaptic integration of newly generated granule cells into the adult hippocampal circuitry. The release of the N-methyl-D-aspartate receptor coagonist D-serine by astrocytes promotes the activity-dependent synaptic integration of new neurons. It has been reported that inhibiting astrocytic D-serine release through the transporter Slc1a4 rescues synaptic damage after brain injury (Tapanes et al., 2022; **Figure 8**). In another study, Shen et al. (2016) reported that deleting MyD88 or suppressing Erk 1/2 in astrocytes rescued lipopolysaccharide-induced developmental abnormalities of excitatory synapses and restored enhanced seizure sensitivity. Indeed, previous studies have identified several astrocyte-derived molecules that are necessary and sufficient to promote excitatory synapse development, such as thrombospondins, Sparcl-1/hevin, glypicans, and chordin-like 1 (Perez-Catalan et al., 2021; Irala et al., 2024). A clinically available antiseizure medication, gabapentin, can antagonize thrombospondin binding to the alpha-2 delta-1 receptor and powerfully inhibit excitatory synapse formation *in vitro* and *in vivo* (Eroglu et al., 2009). However, many other targets need to be evaluated in epilepsy models for their potential in epilepsy modification.

Existing neural circuits with therapeutic potential

The subiculum is a well-studied brain region in the context of temporal lobe epilepsy and is believed to be crucial for the initiation and propagation of seizures. Fei et al. (2022) demonstrated that the projection between the subiculum and the anterior nucleus of the thalamus bidirectionally modulates hippocampal seizures through enhanced hyperpolarization-activated cyclic nucleotide-gated channel-mediated synaptic transmission. In the case of generalized epilepsy, thalamocortical circuits, involving the thalamus and the cerebral cortex, play a central role. Thalamic astrocytes are key regulators of thalamo-cortico-thalamic oscillations, influencing glutamate and GABA synthesis and clearance, making them significant modifiers of the pathophysiology of epilepsy (Lindquist et al., 2023). Despite not being targeted by current antiseizure medications, thalamic astrocytes represent an important therapeutic target for generalized epilepsy and warrant further research. Other circuits, such as the corticolimbic circuit (de Curtis et al., 2023) and the basal ganglia circuit (Vuong and Devergnas, 2018), are also implicated in seizure generation and propagation. Although the role of astrocytes in these circuits is not fully understood, they remain potential targets for epilepsy modification because of their critical role in maintaining neural circuits.

Limitations

This study has several limitations. First, the focus is primarily on basic research, which is predominantly conducted in rodent models, as clinical data for astrocyte-targeted epilepsy therapies remain scarce. Future research in large animal models will be crucial to validate the safety and efficacy of these strategies before their clinical application. Furthermore, owing to the complexity of molecular mechanisms and space constraints, we emphasize key findings rather than providing exhaustive details on signaling pathways. While this approach allows for a concise overview, it may limit the depth of understanding regarding the mechanisms involved.

Conclusions and Perspectives

Antiseizure medications remain the predominant therapy for epilepsy. However, approximately one-third of patients continue to experience unsatisfactory seizure control and impaired social functioning. For patients with controllable epilepsy, antiseizure medications merely control symptoms but also cause significant side effects. In epilepsy, astrocytes often transform into a reactive phenotype, which impairs their ability to maintain the delicate equilibrium of excitation–inhibition and metabolic homeostasis. Compared with existing antiseizure medications, approaches focusing on astrocytes have considerable potential to address the challenges of drug-resistant epilepsy. Furthermore, these strategies might offer the possibility of modifying or even curing epilepsy, a goal that remains elusive with current antiseizure medications. However, no specific pharmaceuticals targeting astrocytes have been developed for clinical use in epilepsy.

Our review highlights the multifaceted roles of astrocytes in brain function, with a particular emphasis on their involvement in epilepsy pathogenesis and their potential as therapeutic targets. We explore potential therapeutic strategies for modulating astrocytic activity to treat epilepsy, organized around four central objectives: restoring the excitation–inhibition balance, reestablishing metabolic homeostasis, modulating immune and inflammatory homeostasis, and reconstructing abnormal neural circuits. However, translating basic research on astrocytic functions into clinical practice remains a lengthy and challenging process. Identifying translational research avenues with greater clinical potential could help guide resource allocation and future study design.

To assess the current landscape of translational research, we investigated ongoing phase III and phase IV clinical trials for epilepsy treatment registered in the U.S. Clinical Trials Registry (**Table 2**). Nearly half of these studies focus on modulating sodium channels or synaptic neurotransmission to reestablish the balance between excitation and inhibition. Notably, approximately one-third of the research aims to regulate the metabolic homeostasis of the neuronal microenvironment, particularly concerning potassium ions and lipid metabolism, an area increasingly seen as promising for novel therapeutic strategies. As an established metabolic modulation, the ketogenic diet has long demonstrated the benefits of modulating energy balance in epilepsy. With the ongoing advancements in basic research, an increasing number of studies are revealing the metabolic regulatory functions of astrocytes in epilepsy. In line with this, a recent study revealed a distinct astrocyte population within epilepsy foci, named lipid-accumulated reactive astrocytes, characterized by a specific lipid accumulation response (Chen et al., 2023b). Lipid-accumulated reactive astrocytes may

Table 2 | **Summary of ongoing phase III and phase IV clinical trials for epilepsy drug treatments registered with the U.S. Clinical Trials Registry**

Therapeutic strategies	Conditions/diseases	NCT umbers	Interventions	Mechanisms
Restoring excitation/inhibition balance of neuron	Drug-resistant epilepsy	NCT05697614	Valproic acid, carbamazepin, phenytoin	Blocking sodium channels
	Epilepsy	NCT04144439	GABA	Activating GABA receptors
	Nonepileptic, stereotypical and intermittent symptoms in chronic subdural hematomas	NCT04759196	Topamax, levetiracetam	Acting on voltage-dependent sodium channels, GABA receptors, and glutamate receptors
	Primary generalized tonic clonic seizures	NCT06579573	Cenobamate	Blocking sodium channels and positive allosteric modulation of GABA receptors
	Partial-onset seizures	NCT05067634		
	Partial-onset epilepsy	NCT06453213		
	Primary generalized tonic clonic seizures	NCT03678753		
	Childhood absence epilepsy or juvenile absence epilepsy	NCT04666610	Brivaracetam	Binding to synaptic vesicle glycoprotein 2A
Rebuilding metabolic homeostasis	Refractory focal onset epilepsy	NCT06309966	BHV-7000	Activating Kv7.2/7.3 potassium channels
	Idiopathic generalized epilepsy with generalized tonic–clonic seizures	NCT06425159		
	Focal-onset seizures	NCT05716100	XEN1101	Activating Kv7.2/7.3 potassium channels
	Focal-onset seizures	NCT05614063		
	Primary generalized tonic–clonic seizures	NCT05667142		
	Dravet syndrome or Lennox-Gastaut syndrome	NCT05163314	Soticlestat	Inhibiting cholesterol 24-hydroxylase
	Developmental and epileptic encephalopathies	NCT05232630	Fenfluramine	Activating multiple serotonin receptors
Modulating neuroinflammation	Drug resistant epilepsy associated with tuberous sclerosis complex	NCT05534672	Rapamycin	Inhibiting the specific mammalian target of rapamycin
Others	Epilepsy-related cognitive deficits	NCT04419272	Methylphenidate	Inhibiting norepinephrine and dopamine reuptake inhibitor
	Epilepsy	NCT02889627	Fecal microbiota suspension	Modulating the gut-brain axis, reducing neuroinflammation
	Lennox-Gastaut syndrome in children and adults	NCT05219617	Carisbamate	Unknown

GABA: Gamma-aminobutyric acid; Kv: voltage-gated potassium channels.

contribute to drug-resistant epilepsy, with A2AR upregulation potentially playing a role in neuronal hyperexcitability. Future therapeutic approaches targeting lipid-accumulated reactive astrocytes could open new pathways for treating patients with drug-resistant epilepsy. Another recent study revealed that the metabolism of astrocytic adenosine triggered glucose metabolism and lactate release via the cAMP signaling pathway, which is crucial for regulating cerebral energy metabolism and influences memory and sleep functions (Theparambil et al., 2024).

Gene therapy has emerged as a compelling area for treating drug-resistant epilepsy. Lentini et al. (2021) demonstrated that retrovirus-mediated expression of Ascl1 and Dlx2 in reactive hippocampal astrocytes within the epileptic hippocampus resulted in efficient reprogramming of these astrocytes into interneurons. These reprogrammed interneurons functionally integrate into epileptic networks and form GABAergic synapses with dentate granule cells. Similarly, Zheng et al. (2022) reported that reactive astrocytes in the hippocampal CA1 region could be effectively converted into GABAergic neurons through the overexpression of the neural transcription factor NeuroD1. Together, these studies underscore the theory of targeting astrocytes through metabolic regulation and genetic reprogramming. Advancing our understanding of astrocyte function in epilepsy not only enhances our insights into the underlying mechanisms of the disease but also opens avenues for more precise and effective treatments in clinical practice. Despite promising therapeutic targets, there are potential challenges associated with translating the identified therapeutic targets into clinical treatments. A primary limitation lies in the substantial physiological, anatomical, and genetic differences between animals (commonly rodent models) and humans. While animal models of epilepsy provide essential insights, they do not fully capture the complexity and heterogeneity of the human condition. Consequently, treatments that demonstrate efficacy in animal models may not yield comparable results in humans owing to these interspecies differences. Moreover, the clinical presentation of epilepsy is often compounded by comorbidities such as cognitive decline or psychiatric disorders, which add layers of complexity to treatment approaches. Animal models typically lack these associated conditions, meaning that the therapies developed and validated in preclinical studies may not adequately address the multifaceted clinical profile of epilepsy patients. This disparity between model conditions and real-world cases underscores the need for more comprehensive research to address these limitations. Tailoring therapeutic approaches to better mirror the human clinical context remains a crucial step in advancing translational efforts and improving treatment outcomes for epilepsy.

Future research on targeting astrocytes to regulate epilepsy could explore the following avenues.

Elucidating the detailed mechanisms by which reactive astrocytes contribute to epilepsy progression is crucial. For example, both the upregulation and downregulation of AQP4 have been reported in epilepsy, highlighting a significant inconsistency that points to the need for further studies. Recent studies have indicated the subcellular redistribution of AQP4 in epilepsy (Alvestad et al., 2013; Szu and Binder, 2022). However, it remains unclear whether this redistribution is a cause or consequence of epilepsy. Therefore, a more comprehensive understanding of the involvement of reactive astrocytes in the mechanisms of epileptogenesis is imperative for identifying pivotal and effective therapeutic targets.

Development of specific imaging strategies for reactive astrocytes: Another critical aspect is discerning how and when transiently activated astrocytes, which initially help limit injury, transition into chronically activated states that contribute to neural damage. Gaining insights into the timing and mechanisms of this transformation is essential for creating effective strategies to counteract it. Positron emission tomography holds promise for noninvasive visualization of reactive astrocytes. Such imaging can serve not only as a diagnostic marker but also as an indicator for therapeutic evaluation and prognosis.

Innovative approaches for modulating reactive astrocytes: In addition to conventional drug therapies, novel noninvasive therapies targeting astrocytes with fewer side effects are under preclinical research. For example, transcranial magnetic stimulation has been reported to alleviate reactive astrogliosis and the overproduction of proinflammatory factors in models of Parkinson's disease and ischemia (Hong et al., 2020; Kang et al., 2022). Similarly, low-frequency ultrasound has demonstrated the ability to modulate the neural network by acting on transient receptor potential channels in astrocytes (Oh et al., 2019). Additionally, the emergence of magnetomechanical stimulation and bioactive engineering offers a promising avenue for remotely and selectively controlling astrocytes (Gong et al., 2022).

In summary, this review strives to deepen our understanding of the pivotal role of astrocytes in epilepsy and to highlight emerging therapeutic targets. Our primary objective is to alleviate the burdens endured by patients with drug-resistant epilepsy and to move the concept of precision medicine into practical application.

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