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The role of astrocytes in epileptic disorders

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Abstract

Epilepsy affects about 1% of the population and approximately 30% of epileptic patients are resistant to current antiepileptic drugs. As a hallmark in epileptic tissue, many of the epileptic patients show changes in glia morphology and function. There are characteristic changes in different types of glia in different epilepsy models. Some of these changes such as astrogliosis are enough to provoke epileptic seizures. Astrogliosis is well known in mesial temporal lobe epilepsy (MTLE), the most common form of refractory epilepsy. A better understanding of astrocytes alterations could lead to novel and efficient pharmacological approaches for epilepsy. In this review, we present the alterations of astrocyte morphology and function and present some instances of targeting astrocytes in seizure and epilepsy.

KEYWORDS

antiepileptic, astrocyte, epilepsy, glia, seizure

1 | INTRODUCTION

Repeated unprovoked epileptic seizures are defined as epilepsy (Thijs et al., 2019). Epilepsy affects about 46 million people in the world (Beghi, 2020). Epileptogenesis occurs when the neuronal network shifts to make recurrent seizures after an initial insult or makes more vigorous frequent seizures in chronic epilepsy (Engel & Pitkänen,

2020). Dysregulation of water and ion channel expression, variations in the secretion of neuroactive molecules, and increased activation of inflammatory pathways, as well as reactive gliosis, are characteristic features in epilepsy (Nickels & Noe, 2021; Rajabian et al., 2022). Considerable alteration in shape and function of glial cells occurs in various kinds of epilepsy. The central nervous system (CNS) is composed of different kinds of glial cells including astrocytes, oligodendrocytes, ependymal cells, microglia, and

Bergmann glia (Foresti et al., 2011; Patel et al., 2019). Glial cells may direct a feeding mechanism, signal transduction from blood to neurons, removal of synaptic glutamate, neuronal path finding, and the sequestration and redistribution of K^+ ion (Foresti et al., 2011; Trosclair et al., 2021). The K^+ long-range spatial buffering conducted by glia is a parallel synchronizing and/or spreading mechanism during paroxysmal oscillations (Chung et al., 2013). Glial cells deliver neuroactive molecules and adjust synaptic transmission through modifications of ion channels, gap junctions, receptors, and transporters (Binder & Carson, 2013).

There is a bidirectional flow of information between neurons and glial cells in the CNS (Héja et al., 2012; Matejuk & Ransohoff, 2020). A variety of processes called neurotransmitter cycles happen at the neuroglial connections between the glutamatergic and gamma-aminobutyric acid (GABA)-ergic synapses. For instance, the cytoplasm of astrocytes contains brain glutamine synthetase (GS) which is particularly enriched in astrocyte processes in specific parts of the neuropil. GS is the only enzyme in the mammalian brain which converts glutamate and ammonia to glutamine (Alemanno, 2020; Mazaud et al., 2019). The intracellular localization of GS in astrocytes is altered in mesial temporal lobe epilepsy (MTLE) (Eid et al., 2013). Furthermore, astrocytes end-feet around vessels contribute to making the blood–brain barrier (BBB) which prevents the entry of most blood constituents to the brain. It has been argued that direct contact between astrocytes and endothelial cells or humoral factors released from astrocytes is required to induce BBB properties (Heithoff et al., 2021; Kadry et al., 2020). It has also been assumed that permeability alteration of BBB is involved in epileptogenesis (Dadas & Janigro, 2019).

1.1 | Astrocytes in epilepsy

There is some evidence that astrocytes have a role in seizure and epilepsy. It has been suggested that epilepsy has an astrocytic origin because direct stimulation of astrocytes causes prolonged neuronal depolarization and epileptiform discharges (Chan et al., 2019; Fellin & Haydon, 2005). Reactive astrocytes in epileptic tissue either promote or inhibit seizure development through different specific mechanisms (Chan et al., 2019; Wetherington et al., 2008). For example, downregulation of inward rectifier K^+ channels (Kir4.1 channel) characterizes transformed astrocytes in the epileptogenic tissue (Chu-Shore et al., 2010; Kinboshi et al., 2020) and aquaporin (AQP4)-null mice show reduced $[Ki]_o$ buffering and prolonged duration of induced seizures (Binder et al., 2006; Strohschein et al., 2011). A better understanding of astrocytes alterations

could lead to novel and efficient pharmacological approaches for epilepsy. In this review, we underline the alterations of astrocytes and summarize some instances of targeting astrocytes in seizure and epilepsy.

2 | ASTROGLIOSIS AND ASTROGLIAL DEATH IN EPILEPSY

Astrogliosis refers to the morphological, biochemical, and functional changes of astrocytes that occur in response to brain insults or injuries. The changes include hypertrophy and up-regulation of the intermediate filament glial fibrillary acidic protein (GFAP), reversible alterations in gene expression, and pronounced cell proliferation with compact scar formation and permanent tissue rearrangement (Robel & Sontheimer, 2016; Sofroniew, 2014). Astrogliosis is well known in MTLE, the most common form of refractory epilepsy (Robel & Sontheimer, 2016). One of the typical features of temporal lobe epilepsy and other epilepsy syndromes is hippocampal sclerosis (Lee et al., 2021). In the sclerotic hippocampus, for instance, Na^+ channels are augmented while Kir4.1 channels are reduced; thus, action potential generation is adjusted. Furthermore, the glutamine synthetase is decreased and glutamate dehydrogenase is increased in the sclerotic hippocampal tissue. The expression of many inflammatory and immune-related molecules is also upregulated in astrocytes (Aoki et al., 2019; Chan et al., 2019). It also seems that the chemical signaling in epileptic tissue is augmented, the association of water and K^+ equilibrium is disturbed and the microenvironment at the border between astrocytes and microvasculature is deteriorated (Wetherington et al., 2008).

The morphological, biochemical, and functional modifications which occur in astrogliosis may make astrocytes resistant to different harmful stimuli. Astroglial death has also been reported following status epilepsy (SE) and kainic acid-induced epilepsy in CA1 (Ko et al., 2016; Revuelta et al., 2005). Astroglial apoptosis (Hyun et al., 2017) and autophagic astroglial death (clasmatodendrosis) have also been reported after SE in the molecular layer of the dentate gyrus and the stratum radiatum in the CA1 (Ryu et al., 2011). The regional-specific astroglial death is independent of hemodynamics. Evidence indicates that the differential mitochondrial dynamics in astrocytes play a key role in the regional-specific astroglial death. The mitochondrial dynamics is highly correlated with dynamin-related protein 1(DRP-1) which is a mitochondrial fission protein (Ko et al., 2016). Inhibition of DRP-1 has exerted protective effects on hippocampal neurons in pilocarpine-induced seizures in rats possibly through reducing the cytochrome c (Cyt C) release, apoptosis-inducing factor

(AIF) translocation, and prevention of mitochondrial-dependent apoptosis pathway (Xie et al., 2013).

3 | ASTROCYTES AND GLUTAMATE/GABA TRANSPORTERS IN EPILEPSY

Neuron–astrocyte interactions are important in the excitatory/inhibitory balance. Interruption of this balance may play a role in the abnormal neuronal activity in seizures (Verdugo et al., 2019). Glutamate released from astrocytes not only enhances neuronal irritability by a feed-forward mechanism during seizure-like events (SLE) but also affects the Hebbian plasticity at single synapses (Perea & Araque, 2007) and produces coordinated activity in neuronal pools (Fellin & Haydon, 2005; Mederos et al., 2018). Following BBB dysfunction, activated astrocytes show reduced levels of mRNA encoding for the astrocytic glutamate transporters of the solute carrier family 1 subfamily A (SLC1A) members, SLC1A2 and SLC1A3. The enzymes such as glutaminase and glutamine synthetase are also down-regulated in astrocytes (Heinemann et al., 2012; Swissa et al., 2019). Reduction of the glutamate uptake in transformed astrocytes may also interrupt the production of glutathione. Astrocytes use glutamate to uptake cystine for synthesizing glutamylcysteine, which is released from astrocytes for the synthesis of glutathione in neurons. Down-regulation of neuronal and glial glutathione would lessen the defense mechanisms against free radicals and may result in increased damage. Furthermore, glutamine decrement may impede the detoxification of ammonium. Ammonium disturbs Cl2 transporters and may result in the reduction of the GABA-mediated synaptic inhibition (Heinemann et al., 2012; Swissa et al., 2019).

On the other hand, it has been shown that glutamate uptake leads to GABA release from astrocytes which directly affects the irritability action of hippocampal pyramidal neurons. Astrocytic GABA release is mediated by the reverse action of glial GABA transporter (GAT) subtypes, GAT-2 or GAT-3. The activity of the glutamate transporter triggers the reversal of GABA transporters through increasing astrocytic Na^+ concentration. Then, GABA causes tonic inhibition in a network activity-dependent way. This is an example of an in situ negative feedback mechanism by which astrocytes convert the glutamatergic excitation to GABA-ergic inhibition for modifying the excitability of neurons (Héja et al., 2012).

Glutamate and GABA uptake by astrocytes is an example of active hyperemia that induces a local increase in cerebral blood flow (CBF) through a variety of mechanisms. Interestingly, astrocytes exert a slow indirect role in these mechanisms whereas the neurons play a fast direct effect (Attwell et al., 2010; Banks et al., 2018; Marina et al., 2020). The association of calcium dynamics in CBF regulation could explain the major involvement of astrocytes (80%) rather than neurons in CBF. Indeed, the evidence showed that the vast majority of astrocytes responded with a calcium elevation to ictal but not interictal discharges (Gómez-Gonzalo et al., 2010). Using a computational method, it was found that when the interictal discharge was sufficiently important, astrocytes contribution was already present (Blanchard et al., 2016).

4 | ASTROCYTES, GAP JUNCTIONS, CONNEXINS, AND PANNEXINS IN EPILEPSY

Gap junctions (GJ) have been found to play an important role in neuronal synchronization and seizure induction (Fonseca et al., 2002; Li et al., 2019; Onodera et al., 2021). Knocking out (dKO) of the glial connexin (Cx) 30 and 43 has revealed that GJ communication between astrocytes is required for glucose or lactate transport to astrocytes which is essential to maintain excitatory synaptic transmission and epileptiform activity (Li et al., 2019; Rouach et al., 2008; Wallraff, 2006). GJ communication is also involved in propagating apoptotic signals (Y. Wang et al., 2012), a process that is significant in severe seizure activity (Engel & Henshall, 2009). Recently, using dKO mice it was revealed that animals lacking oligodendrocytic Cx32 and astrocytic Cx43 displayed seizures, motor impairment, and early mortality (Magnotti et al., 2011). Investigations of GJ expression in epileptic brains in humans either reported no change (Elisevich et al., 1997) or elevated levels of glial Cx mRNA and protein (Collignon et al., 2006; Naus et al., 1991). The role of pannexins has not been studied as much as Cx. Studies suggest that blocking Panx1 channels reduces excitability and can be anticonvulsant. They may also exert compensatory, overlapping, or exclusive physiological roles compared to those of Cx in seizure models (Aquilino et al., 2019).

5 | ASTROCYTES AND CYTOKINES IN EPILEPSY

In contrast to the well-known role of microglia as antigen-presenting cells (APCs), the role of astrocytes in antigen presentation is still unclear (Aronica et al., 2012). Studies suggested that while microglia may activate both Th1 and Th2 cells (T helper 1 and 2 cells, respectively), astrocytes mainly stimulate Th2 responses, providing

homeostatic mechanisms which may limit brain inflammation (F. Aloisi et al., 2000; Francesca Aloisi et al., 1998). Astrocytes have been shown to initiate, regulate, and amplify the immune-mediated mechanisms involved in different CNS diseases including epilepsy (Kwon & Koh, 2020; Seifert et al., 2010). They are also the target of inflammatory molecules which may aggravate astrogliosis and intensify the pro-epileptogenic inflammatory signaling through the activation of specific receptors and related signaling pathways (Giovannoni & Quintana, 2020; Kwon & Koh, 2020). Based on in vitro studies, astrocytes (particularly reactive astrocytes) can generate cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, transforming growth factor-beta (TGF)-β, and chemokines such as monocyte chemoattractant protein-1 (MCP-1) and chemokine C- motif ligand 2 (CCL2), which are highly expressed in both the experimental and human epileptogenic brain tissue (Aronica et al., 2012; Giovannoni & Quintana, 2020). In an inflammatory epileptic encephalopathy of childhood, that is, Rasmussen's encephalitis (RE), expression of major histocompatibility complex (MHC) class I molecules have been reported to increase in astrocytes (Bauer et al., 2007). Therefore, an MHC class I-restricted T-cell response has been proposed as a possible mechanism for the astrocytic breakdown in RE (Bauer et al., 2007).

Reactive astrocytes also contain complement components and express complement-regulatory proteins as well as complement receptors (Farina et al., 2007; Giovannoni & Quintana, 2020). Cytokine production is adjusted by complement system products such as C3 and cytokines such as IL-1β may induce complement factor expression in human astrocytes (Bonifati & Kishore, 2007; Morotti et al., 2018). Meanwhile, astrocytes induce inhibitory factors such as complement factor H (CFH) which can modify the inflammatory pathway (Giovannoni & Quintana, 2020; Griffiths et al., 2009). An extensive and complex cross-talk between complement and Toll-like receptors (TLRs) has been proposed (Hajishengallis & Lambris, 2010; Kumar, 2019). Upregulation of IL-1R1 or TLRs in reactive astrocytes in the human brain has been reported in epilepsy (Aronica et al., 2012). It has been demonstrated that the TLR4 and its endogenous ligand, high mobility group box-1 (HMGB1), are overexpressed in reactive astrocytes in human temporal lobe epilepsy (TLE) (Kan et al., 2019; Maroso et al., 2010). Following release from neurons, HMGB reacts with TLR4 to develop seizures which in turn induces an additional wave of HMGB1 release from activated astrocytes and microglia. Consequently, it leads to a positive feedback cycle of seizures and inflammation which can be the core mechanism of recurrent seizures (Vezzani et al., 2011).

6 | ASTROCYTES AND PURINERGIC RECEPTORS IN EPILEPSY

Purinergic receptors play a critical role in neuron-glia communication and neuroinflammation (Agostinho et al., 2020; Kovács et al., 2015). There is a general agreement that extracellular and synaptic adenosine (Ado) levels are mainly regulated by astrocytes. Ado and non-Ado nucleosides may be transported through neuronal and glial cell membranes by two types of nucleoside transporters, the equilibrative nucleoside transporter family (ENT) and the sodium-dependent concentrative nucleoside transporter family (CNT) (Young et al., 2013). The astrocytic cycle that maintains the extracellular Ado levels consists of the release of ATP that is broken down to Ado, direct release and uptake of Ado through ENTs, and conversion of intracellular Ado to Ado phosphates. Adenosine receptors are coupled with "inhibitory" G-proteins (Gi) or "stimulatory" G-proteins (Gs) such as A1/A3 and A2A/A2B receptors, respectively. The G-protein-coupled A1, A2A, A2B, and A3 receptors express on both neuronal and glial cells (Dias et al., 2013; Fredholm, 2012; Jennings et al., 2001; Kovács et al., 2011; Sperlágh & Sylvester Vizi, 2011; Zarrinmayeh & Territo, 2020). In animal models of human absence epilepsy in Wistar albino Glaxo/Rijswijk (WAG/Rij) (D'Alimonte et al., 2009) and genetic absence epilepsy rat from Strasbourg (GAERS) rats (Ekonomou et al., 1998), kainic acid-induced epilepsy (Ekonomou et al., 2000), as well as in the epileptic temporal cortex in human (Glass et al., 1996), distribution of A2A and/or A1 receptor density is altered. Thus, Ado receptors play a role in epileptic activity (Kovács et al., 2015). The ENTs on astrocytes efficiently convert Ado to adenosine monophosphate (AMP) by adenosine kinase (ADK); thereby, astrocytes remove Ado from the extracellular space and stop adenosinergic signaling (Fredholm, 2012). ADK is predominantly localized to astrocytes and phosphorylation of ATP to AMP by ADK plays a major role in the Ado metabolism (Boison et al., 2010). The expression of ADK can be adjusted by inflammatory molecules, such as IL-1β, providing potential modulatory crosstalk between the astrocyte-based adenosine cycle and inflammation (Aronica & Crino, 2011).

7 | ASTROCYTIC PH DYNAMICS IN EPILEPSY

Previously, neuronal acidification had been established during seizures (Raimondo et al., 2015, 2016). Recently, using genetically encoded pH sensors, it has been demonstrated that astrocytes are alkalinized during seizures. Furthermore, astrocytes have shown faster pH change

than neurons. The alkalinization is correlated with changes in membrane potential and generated by an electrogenic $Na^+/HCO3^-$ co-transporter. Moreover, the astrocytic pH alterations are more closely associated with network activity than neuronal pH changes (Raimondo et al., 2016).

8 | ASTROCYTE DYSFUNCTION IN TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder due to autosomal dominant mutations of either the TSC1 or TSC2 genes which are among the most common genetic causes of epilepsy. Patients with TSC demonstrate epilepsy in 80–90% of cases. They demonstrate multiple seizure types which are often resistant to antiepileptic drugs (AEDs) (Gupta et al., 2020). The disease usually occurs in the first year of life (Curatolo et al., 2018). The number of astrocytes is increased in tubers compared to the control and also neighboring brain tissue. There are morphological and biological differences in the subpopulation of astrocytes in tubers (Sosunov et al., 2008). Astrogliosis in tubers is composed of a combination of gliotic astrocytes similar to what is seen in hippocampal sclerosis and also reactive astrocytes which are vimentin immunoreactive and show the mammalian target of rapamycin (mTOR) activity (Wong, 2019). Proteins encoded by TSC1 and TSC2 function as negative regulators of the mTOR signaling pathway. Therefore, loss of function mutations of either TSC1 or TSC2 is followed by constitutive mTOR activation (Wong & Crino, 2012). The phosphorylated S6 protein, a downstream mTOR substrate, has been observed in dysplastic astrocytes which confirms that astrocytosis could reflect direct effects of mTOR pathway activation (Talos et al., 2008). An increase in vascular endothelial growth factor A (VEGFA) expression has been reported within cortical tubers of people with TSC (Parker et al., 2011). Expression reduction of glutamate transporters, glutamine synthetase, and the Kir 4.1 has been also observed in gliotic astrocytes in tubers. Abnormalities in the astrocytic regulation of glutamate and potassium have also been recognized in animal models of TSC and human tuber specimens resected during epilepsy surgery (Talos et al., 2008; Wong & Crino, 2012).

9 | BLOOD–BRAIN BARRIER DISRUPTION AND EPILEPSY

Following the BBB illness, the neuronal network restructures itself because of the renovation or activation of glia.

In the case of the experimental disintegration of the BBB of the rat neocortex, the delayed development of paroxysmal hypersynchronous activity which is indicative of epileptogenesis is recorded ex vivo and in vivo. For instance, direct brain exposure to serum albumin leads to albumin uptake into astrocytes via transforming growth factor-beta receptors (TGF-β Rs). Albumin uptake is followed by down-regulation of Kir4.1 and aquaporin 4 channels (AQP4) in astrocytes, resulting in reduced buffering of extracellular potassium (David et al., 2009; Heinemann et al., 2012). This, in turn, leads to activity-dependent increased extracellular potassium, leading to facilitated *N*-methyl-d-aspartate (NMDA)-receptor-mediated neuronal hyperexcitability and eventually epileptiform activity (Ivens et al., 2007; Seiffert et al., 2004).

The vascular lesion has also been proposed in the pathogenesis of post-traumatic epilepsy (PTE) in humans (Sakai et al., 2018; Tomkins et al., 2011). It has been reported that the VEGFA is up-regulated in reactive astrocytes in human epileptogenic tissue (B. Bauer et al., 2008; Morin-Brureau et al., 2011; Rigau et al., 2007). The integrity of the BBB changes by VEGFA-signaling pathways (Schoch et al., 2002; Thanabalasundaram et al., 2010). Following hypoxia or inflammation, VEGFA is increased by induction of transcription factors including hypoxia-inducible factor-1 (HIIF-1), activation protein-1 (AP-1), specificity protein 1 (SP-1), signal transducer, and activator of transcription factor-3 (STAT3). Seizures can also induce all of these transcription factors in addition to VEGFR-2 receptor activation (Morin-Brureau et al., 2011). The endothelial cells and neurons express VEGFR-2. VEGFA-VEGFAR-2 signaling leads to the variation of tight junctions and vascular remodeling via Src and PKC downstream pathways (Figures 1 and 2) (Morin-Brureau et al., 2011).
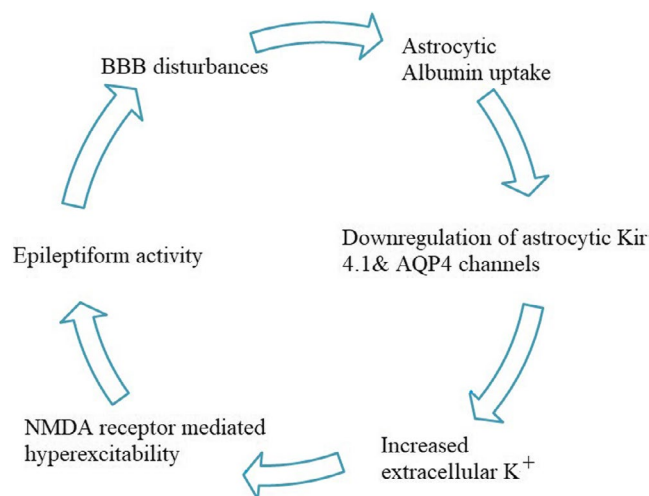

FIGURE 1 Schematic representation of the relationship between BBB disturbance and epileptiform activity
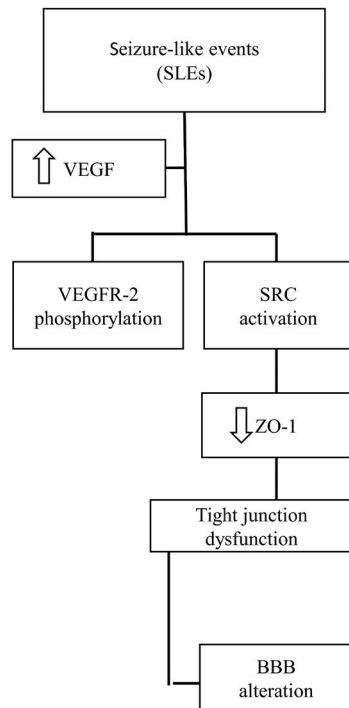
FIGURE 2 Cascade of events leading to blood brain barrier disruption after seizure like events. VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor 2; SRC, xxx; ZO-1, zonula occludense 1; BBB, blood brain barrier

10 | ASTROCYTES AND INFLAMMATION AND IMMUNITY IN EPILEPSY

The beneficial effects of steroid-containing and other anti-inflammatory drugs in the treatment of epilepsy led to the hypothesis that inflammation plays a crucial role in epilepsy (Vezzani et al., 2011). Chronic brain inflammation was initially noted in RE, a kind of childhood epilepsy (Vezzani et al., 2011). Inflammation can be not only a cause but also a consequence of epilepsy (Vezzani et al., 2011). Seizure predisposition has shown a dramatic reduction in mice with overexpressed IL-1Ra, an endogenous antagonist of IL-1B, in astrocytes (Teresa Ravizza et al., 2006). Autoimmune disorders also led to seizure and epilepsy, for example, in RE, and in severe intractable seizures, glutamate receptor 3 antibodies have been seen (Mantegazza et al., 2002). There is astrocytic apoptosis and loss in cortical and white matter areas in RE and astrocytes express MHC class 1, moreover, granzyme-B+ lymphocytes are close to astrocytes bordering astrocyte-deficient lesions. Granzyme-B+ granules have polarization facing the astrocytic membrane (J. Bauer et al., 2007).

Elevation of inflammatory cytokines production such as IL-1β, IL-6, and TNF-α were reported in patients and animal models of TLE (Vezzani et al., 2011, 2013), in the hippocampus 1 day after SE induction by electric stimulation (De Simoni et al., 2000) and about 3 hours after developmental febrile SE (Patterson et al., 2015). Neurons, microglia, astrocytes, and endothelial cells produce inflammatory cytokines (Benson et al., 2015). Furthermore, astrocytes may play a role in the modulation of cytokine release from microglia (Hiragi et al., 2018). Following administration of TLR4 antagonist, acute seizures were reduced in kainic acid-induced epilepsy in mice. It has been suggested that astrocytes express TLR4 following kainic acid-induced seizures (Maroso et al., 2010).

11 | ASTROCYTES IN FEBRILE SEIZURES

When a previously healthy child sustains severe refractory SE after a brief recovery from a short febrile disease, and infectious encephalitis is ruled out, then the condition can be suspected as febrile infection-related epilepsy syndrome (FIRES) (van Baalen et al., 2017). FIRES is a sporadic condition. SE appear at the days following fever initiation in FIRES which is contrary to febrile SE. About 5% of SE cases are categorized as FIRES and in adults, these are called malignant or new-onset SE (Vezzani et al., 2015).

It has been suggested that neuroinflammation plays a role in FIRES-associated epileptogenesis in animal models of infection (Galic et al., 2012; Riazi et al., 2010), as well as febrile and afebrile SE later developing epilepsy (Dubé et al., 2010). Neuroinflammation reduces seizure threshold rather than triggering seizures, thus FIRES shows a delayed onset (van Baalen et al., 2017).

It has been indicated that astrocytes initiate, adjust and enhance immune-mediated responses in CNS human diseases such as epilepsy (Farina et al., 2007; Seifert et al., 2010). It has been reported that astrocytes mediate mainly Th2 reactions, triggering homeostatic mechanisms to reduce brain inflammation (Aloisi et al., 2000).

12 | ASTROCYTES AND HIPPOCAMPAL SCLEROSIS

One of the characteristic features of refractory temporal lobe epilepsy is hippocampal sclerosis (HS) (Sendrowski & Sobaniec, 2013). There is pyramidal cell loss in CA1, CA3 and around end-folium in classical HS, however, CA2 cells are maintained. In certain kinds of HS, pyramidal cell loss occurs in all hippocampal fields (total hippocampal sclerosis), or only around end-folium (end-folium hippocampal sclerosis) (Thom, 2004).

Furthermore, degeneration of neurons, gliosis, sprouting of mossy fibers, and dispersion of dentate gyrus granule cells are seen in HS (MD et al., 2002). It has been reported that astrocytes have a specific structure and function in HS (D. K. Binder & Steinhäuser, 2006). It has been reported that the activity of excitatory sodium currents is enhanced through the cell membrane of hippocampal astrocytes in patients with HS (Bordey & Spencer, 2004). Increased expression of genes encoding for proteins leading to glutamate release was noted on the surface of astrocytes in hippocampal samples of patients with HS (T.-S. Lee et al., 2007).

13 | TARGETING ASTROCYTES FOR THERAPEUTIC APPROACHES IN EPILEPSY

Because of the bidirectional flow of information between neurons and glial cells and glial–glial or glial microenvironmental compartments, there are various prospective strategies for developing/ testing new anti-epileptic drugs. Of note, glutamate plays a pivotal role in the initiation and propagation of seizures. It has been suggested that increased glial glutamate transporter EAAT2 which enhances glutamate uptake, is a potential therapeutic approach for treating epilepsy. Kong et al. (2012) reported: (1) mortality rates decreased in EAAT2 transgenic mice after pilocarpine SE, (2) increased EAAT2 attenuated hippocampal neuronal loss after SE, (3) increased EAAT2 inhibited neurogenesis and mossy fiber sprouting after SE, and (4) increased EAAT2 reduced spontaneous recurrent seizures after SE (Kong et al., 2012).

Furthermore, astrocytes control the activity of Ado receptors that are expressed in neurons, astrocytes, microglia, and oligodendrocytes (Kovács et al., 2015). Adenosine and its analogs, together with non-adenosine (non-Ado) nucleosides (e.g., Guanosine (Guo), Inosine and Uridine) have shown anti-seizure activity. Adenosine kinase inhibitors, Ado uptake inhibitors, and Ado-releasing implants have also shown beneficial effects on epileptic seizures (Kovács, Kékesi, Juhász, Barna, et al., 2014; Kovács et al., 2015; Kovács, Kékesi, Juhász & Dobolyi, 2014). The Ketogenic diet, a therapeutic regimen in refractory epilepsy, reduces plasma glucose levels and also suppresses seizure through A1 receptor activation and reduction of ADK expression. The pharmacological blockade of ADK has also exerted a powerful antiepileptic effect in several models of epilepsy (Kovács et al., 2015; Wang & Li, 2020). Additionally, activation of Guo receptors may reduce extracellular glutamate level and glutamate-induced excitability by triggering glial glutamate uptake (de Oliveira et al., 2004; Frizzo et al., 2003; Kovács, Kékesi, Juhász &

Dobolyi, 2014; Schmidt et al., 2007; Torres et al., 2010). It has been shown that extracellular guanosine adjusts extracellular adenosine levels (Jackson et al., 2013).

Regarding network communication, the expression of the astrocytic gap junction proteins connexin 30 and 43 is reduced in the BBB-induced epileptogenic cortex. Carbenoxolone is a broad-spectrum GJ blocker with additional anti-inflammatory and mineralocorticoid-like properties (Li et al., 2019; Nilsen et al., 2006). In vitro and in vivo experiments have shown that carbenoxolone can decrease seizure-like activities in different types of epilepsy models (Franco-Pérez et al., 2018; Gigout et al., 2006; Sefil et al., 2012; Ventura-Mejía & Medina-Ceja, 2014). For example, blockade of the GJ with carbenoxolone has decreased the duration of seizures and the amplitude of the seizure discharges in 4-aminopyridine induced epilepsy in anesthetized rats (Gajda et al., 2003). Furthermore, local administration of carbenoxolone in an in vivo model of refractory epilepsy in un-anesthetized rats also reduced the percentage of seizure time (Nilsen et al., 2006).

Blocking the specific inflammatory pathways which are activated during epileptogenesis may also decrease the severity and the occurrence of spontaneous seizures (Aronica et al., 2012). Microglia and astrocytes are the main sources of IL-1β in epileptogenic brain tissue and IL-1R1 is overexpressed in both neurons and glia. Using VX-765 which is a selective interleukin converting enzyme inhibitor has inhibited the endogenous production of IL-1β and interfered with the promotion of generalized motor seizures in stimulated rats but not fully kindled rats in a kindling model (T. Ravizza et al., 2008). Furthermore, cannabinoid (CB) receptors, as mediators of endocannabinoid signaling, have demonstrated an immunomodulatory effect on astrocytes (Fields et al., 2020; Sheng et al., 2005). As mentioned in Section 9, TGF-βR is a putative candidate for albumin uptake and its expression is enhanced following brain insults. TGF-βR1 kinase activity inhibitor, SB431542, has been reported to prevent the albumin uptake (Ivens et al., 2007; Morganti-Kossmann et al., 2002). Therefore, targeting the TGF-βRs may have therapeutic advantages in posttraumatic epilepsy syndromes. There can be other potential targets such as understanding the mechanisms by which GS is regulated which may lead to novel therapeutic approaches to MTLE, the frequently refractory epilepsy to antiepileptic drugs.

14 | DISCUSSION

As mentioned above, various likely mechanisms are leading to recurrent seizures and epilepsy. Astrocytes are involved in brain inflammation and inflammation is not only the cause but also the consequence of epilepsy, providing a vicious

cycle and recurrence of seizures. Also, astrocytes serve as both sources and targets of related inflammatory cell signaling receptors (Aronica et al., 2012). IL-1β through IL-1R type 1 receptors increases the extracellular glutamate release by inhibiting astrocytic glutamate reuptake and increasing glial release via induction of TNF-α, glutamate, in turn, enhances the brain excitability (Bezzi et al., 2001). Inhibition of the production of IL-1β in astrocytes has been shown to decrease the spike and wave discharges in rats with genetic absence epilepsy (GAERS) (Akin et al., 2011). During the past decade, the key role of astrocytes in the CNS innate immune system has been more elucidated (F. Aloisi et al., 2000; Farina et al., 2007). Astrocyte immune-inflammatory dysregulation is a common factor in a variety of epilepsy models. Therefore, pharmacological blocking of inflammatory pathways may reduce the intensity and frequency of spontaneous seizures (Aronica et al., 2012). It has been observed that even adjunctive therapy with certain anti-inflammatory drugs such as statins may exert beneficial effects in SE prognosis in the clinical setting (Vezzani et al., 2015). When the bioelectrical activity of a group of cerebral cortical neurons increases and their activity is hypersynchronized, epileptic seizures occur (Avoli et al., 2005). The gap junctions between adjacent neurons and astrocytes are important ultrastructural elements in hypersynchronization (Sendrowski & Sobaniec, 2013). Therefore, blocking the gap junctions may reduce seizure severity or frequency.

It has been assumed that seizures give rise to seizures (Gillespie, 1902). Accordingly, it has been observed that HS is not only the cause but also the result of drug-resistant epilepsy (Sendrowski & Sobaniec, 2013). Thus, prevention and treatment of seizures lead to better outcomes and prognoses. Astrocytes are the major type of glia in the CNS with bidirectional flow of information between adjacent cells and a variety of receptors and neurotransmitters so\ that targeting astrocytes can be a promising approach in ameliorating epileptic conditions.

15 | CONCLUSION

As above mentioned, astrocytes are active contributors of ions concentration such as Ca^{2+} and K^+ in the brain. They are also the main regulators of glutamate and GABA, and exert an important regulatory effect on pH. Considering the roles of the mentioned ions, neurotransmitters, and pH in the neuronal activity in the brain, the roles of astrocytes in epilepsy are conceivable. Astrocytes also have important roles in the function of gap junctions and BBB, immunity, inflammation, and regulation of cytokines. Therefore, it is conceivable that astrocytes play a key role in epilepsy and targeting astrocytes can be a new approach in the treatment or prevention of epilepsy.

CONFLICT OF INTEREST

There is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization and Investigation [HP, RA, HM]; Writing – Original Draft, [all authors participated in the writing]; Writing – Review & Editing, [HP, RA, HM, HV]; Supervision, [HP, RA, HM].

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