Astrocytic Ca$^{2+}$ Signaling in Epilepsy

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Epilepsy is one of the most common neurological disorders – estimated to affect at least 65 million worldwide. Most of the epilepsy research has so far focused on how to dampen neuronal discharges and to explain how changes in intrinsic neuronal activity or network function cause seizures. As a result, pharmacological therapy has largely been limited to symptomatic treatment targeted at neurons. Given the expanding spectrum of functions ascribed to the non-neuronal constituents of the brain, in both physiological brain function and in brain disorders, it is natural to closely consider the roles of astrocytes in epilepsy. It is now widely accepted that astrocytes are key controllers of the composition of the extracellular fluids, and may directly interact with neurons by releasing gliotransmitters. A central tenet is that astrocytic intracellular Ca$^{2+}$ signals promote release of such signaling substances, either through synaptic or non-synaptic mechanisms. Accruing evidence suggests that astrocytic Ca$^{2+}$ signals play important roles in both seizures and epilepsy, and this review aims to highlight the current knowledge of the roles of this central astrocytic signaling mechanism in ictogenesis and epileptogenesis.

Keywords: astrocyte, epilepsy, calcium signaling, IP3, epileptogenesis, ictogenesis, astrogliosis

INTRODUCTION

Epilepsy is one of the most common neurological disorders – estimated to affect around 1% of the world’s population (Hesdorffer et al., 2011; Neligan et al., 2012; Beghi, 2016). It is a chronic disorder, characterized by sudden, violent perturbations of normal brain function, causing social stigma, morbidity, and risk of premature death. In spite of a multitude of drugs for the treatment of epilepsy, about 30% of patients are not able to control their seizures with seizure suppressing medication (French, 2007; Perucca and Gilliam, 2012).

There is a striking lack of knowledge of the pathophysiological cellular mechanisms at play in epilepsy. For instance, the process transforming normal brain matter to a focus for epileptic seizures – the process of epileptogenesis – is not well understood. Also, the central question of what sets in motion an epileptic seizure – ictogenesis – remains unanswered. Most of the epilepsy research has so far focused on how to dampen neuronal discharges and to explain how changes in intrinsic neuronal activity or neuronal network function cause seizures. As a result, pharmacological therapy has been limited to symptomatic treatment aiming at neuronal targets. Given the expanding spectrum of roles ascribed to the non-neuronal constituents of the brain, it is natural to take a closer look at astrocytes as potential targets for epilepsy treatment.

Astrocytes are critical homeostatic controllers of extracellular glutamate and K$^+$ levels (Rothstein et al., 1996; Larsen et al., 2014; Danbolt et al., 2016). Numerous studies have also demonstrated that astrocytes have important roles in supporting the neurons metabolically...
found that eliciting astrocytic Ca\textsuperscript{2+} signals by photolysis of caged Ca\textsuperscript{2+} and by application of ATP agonist and mGluR5 agonist triggered slow inward currents (SICs) in nearby neurons that were unaffected by application of the neuronal sodium channel blocker tetrodotoxin (Fellin et al., 2004). Soon thereafter, Tian et al. (2005) demonstrated that Ca\textsuperscript{2+} mediated glutamate release from astrocytes during experimentally induced seizure activity triggered slow inward currents (SICs) in neurons. These findings proposed a role for astrocytes in synchronizing neuronal activity and contributing to seizure generation (Tian et al., 2005). Further exploring which astrocytic Ca\textsuperscript{2+} signaling mechanisms were involved in this context, Kang et al. applied IP\textsubscript{3} into astrocytes of the CA1 hippocampal region in rats, and were able to trigger epileptiform discharges in adjacent neurons (Kang et al., 2005). Later, Ding et al. (2007) were able to demonstrate increased astrocytic Ca\textsuperscript{2+} signaling in an in vivo pilocarpine epilepsy model. They proposed that this increase in Ca\textsuperscript{2+} signaling was due to activation of astrocytic metabotropic glutamate receptors, and that this activation led to the release of glutamate from astrocytes that could contribute to neuronal SICs through the activation of extrasynaptic neuronal NMDA receptors. By applying simultaneous patch-clamp recordings and Ca\textsuperscript{2+} imaging in cortical slices of the rat entorhinal cortex, Gómez-Gonzalo et al. (2010) found that Ca\textsuperscript{2+} elevations in astrocytes correlate with initiation and maintenance of focal seizure-like discharges, and postulated a recurrent excitatory loop between neurons and astrocytes in ictogenesis, where astrocytes play a role in recruiting neurons to ictal events, possibly through the release of gliotransmitters (Gómez-Gonzalo et al., 2010).

By using two-photon microscopy and simultaneous astrocyte and neuron Ca\textsuperscript{2+} imaging in the hippocampal CA1 region of awake mice, we were able to show that prominent astrocytic Ca\textsuperscript{2+} transients preceded local hypersynchronous neuronal activity in the emergence of kainate induced generalized epileptic seizures (Heuser et al., 2018). These findings were in agreement with the earlier results from the study of Tian et al. (2005), who also observed stereotypical astrocytic Ca\textsuperscript{2+} signals typically preceding local neurons in the spread of cortical seizure activity. A later work by Díaz Verdugo et al. (2019) similarly demonstrated large and synchronized astrocytic Ca\textsuperscript{2+} signals preceding ictal onset in zebrafish, and proposed that this signaling modulated neural excitation through glutamate release, by gap junction dependent mechanisms. In another in vivo study, Zhang et al. (2019), provided evidence, although correlative, that increased Ca\textsuperscript{2+} concentration in astrocytic endfeet governed precapillary arteriole dilation during epileptic events, suggesting a role for astrocytes in the metabolic support of neurons in seizures. In contrast to these previously mentioned studies, data from another model for focal neocortical seizures in anesthetized rats using bulk-loaded synthetic Ca\textsuperscript{2+} indicators found the astrocytic Ca\textsuperscript{2+} activation to lag behind neuronal activation and to be unnecessary for ictogenesis and the accompanying vascular dynamics (Baïrd-Daniel et al., 2017).

An extensive array of stimuli and corresponding signaling pathways have been shown to trigger intracellular Ca\textsuperscript{2+} signals in astrocytes (Zhang et al., 2019; Caudal et al., 2020). To

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Ictogenesis describes the emergence of seizure activity (Blauwblomme et al., 2014). The interaction between astrocytes and neurons in ictogenesis has only sparsely been investigated and findings are to some extent ambiguous or contradictory, potentially due to different experimental models (Table 1; Tian et al., 2005; Fellin et al., 2006; Gómez-Gonzalo et al., 2010; Baïrd-Daniel et al., 2017; Heuser et al., 2018; Díaz Verdugo et al., 2019). Astrocytes express a plethora of functionally important receptors, transporters and channels, and a role of these cells in ictogenesis is highly suggestive (Aguéhon et al., 2008; Patel et al., 2019; Caudal et al., 2020). Several known astrocyte-neuron interactions involving Ca\textsuperscript{2+} signaling can partake in ictogenesis or in the maintenance of hypersynchronous neuronal activity, possibly by creating excitatory feedback loops (Figure 1; Gómez-Gonzalo et al., 2010; Henneberger, 2017).

Building upon seminal studies demonstrating that astrocytes are able to directly interact with neurons (Nedergaard, 1994; Parpura et al., 1994; Araque et al., 1998; Parpura and Hayden, 2000; Parri et al., 2001; Angulo et al., 2004), Fellin et al. (2006),...
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| Publication | Model | 
|-------------|-------|
| Kang et al., 2005 | Rat hippocampal slices, 4-AP | Fluo-4 AM | Adding IP$_3$ in astrocytes causes ictal neuronal activity due to glutamate, and that astrocytic Ca$^{2+}$ signals occur during 4-AP seizures |
| Tian et al., 2005 | Rat hippocampal slices: 4-AP; zero-Mg$^{2+}$, bicuculline, penicillin Mouse cortex, in vivo, anesthetized: local injection of 4-AP | Fluo-4 AM | Increased astrocytic Ca$^{2+}$ signaling *in vivo* during spread of 4-AP seizures, as well as showing that uncaging Ca$^{2+}$ in astrocytes and extrasynaptic sources of glutamate triggered paroxysmal depolarization shifts |
| Fellin et al., 2006 | Mouse cortical-hippocampal slices: zero-Mg$^{2+}$ and picrotoxin, or 0.5 mM Mg$^{2+}$ and 8.5 mM K$^+$ | Indo-1 AM or OGB-1 AM | A correlation between astrocytic Ca$^{2+}$ and SICs, but activation of extrasynaptic NMDA activation by astrocytes is not necessary for either ictal or interictal epileptiform events |
| Ding et al., 2007 | Mouse, in vivo, anesthetized. Pilocarpine s.c., 350 mg/kg | Fluo-4 AM | Increase in astrocytic Ca$^{2+}$ signals during SE. See also under “Epileptogenesis” |
| Gómez-Gonzalo et al., 2010 | Mouse entorhinal cortex slice: Picrotoxin/zero-Mg$^{2+}$ Whole guinea pig: Bicuculline | Indo-1 AM or Rhod-2 | Astrocytic Ca$^{2+}$ signals are triggered by ictal but not interictal events, and can be inhibited by blocking mGluRs and purinergic receptors. Astrocytic Ca$^{2+}$ signals contribute to the excitation of neurons, and blocking of early ictal astrocytic Ca$^{2+}$ signals prevent spread of ictal activity. |
| Baird-Daniel et al., 2017 | Rat cortex, in vivo, anesthetized. 4-AP. Blocking astrocytic Ca$^{2+}$ signals and gap junctions with fluorooacetate and carbenoxolone, respectively | OGB-1 AM or Rhod-2 AM | Increased Ca$^{2+}$ signals in astrocytes during seizures, but blocking of these did not affect epileptiform discharges or vascular dynamics associated with the seizures |
| Heuser et al., 2018 | Mouse hippocampus, in vivo, unanesthetized, “dual color” Ca$^{2+}$ imaging of hippocampal neurons and astrocytes | GCaMP6f in astrocytes | Prominent astrocytic Ca$^{2+}$ activity preceding local neuronal recruitment to seizure activity in hippocampus |
| Diaz Verdugo et al., 2019 | Zebra fish: PTZ | GCaMP6fs in astrocytes | Large activations of astrocytic Ca$^{2+}$ signals in the pre-ictal state and that astrocytic Ca$^{2+}$ signals contribute to excitation of neurons |
| Zhang et al., 2019 | Mouse cortex, in vivo, anesthetized: local injection of 4-AP | OGB-1 AM | Absolute levels of Ca$^{2+}$ in the astrocytic endfeet correlates with vascular tone during seizures |

Astrocytic calcium signaling in epileptogenesis

| Publication | Model | Ca$^{2+}$ indicator | Main findings |
|-------------|-------|-------------------|--------------|
| Ding et al., 2007 | Mouse cortex, in vivo, anesthetized: Pilocarpine s.c. 350 mg/kg. 3D post SE | Fluo-4 AM | An increase in astrocytic Ca$^{2+}$ signals at day 3 after SE due to mGluR5 signaling. Blocking this hyperactivity attenuated neuronal death |
| Szkold et al., 2015 | Mouse hippocampal slices: intracortical kainate injection. Early epileptogenesis (1, 3, and 7 days after SE) | GCaMPSE | Increased Ca$^{2+}$ signaling in hippocampal astrocytes upon schaffer collateral stimulation at days 1 and 3 after SE mediated by mGluR |
| Umpierre et al., 2019 | Mouse hippocampal slices, at 1–3, 7–9, or 28–30 days after SE | GCaMP5G | mGluR5-mediated Ca$^{2+}$ signaling re-emerges in epileptogenesis |
| Mentioned in Shigetomi et al. (2019); Sato et al.: unpublished report | 4 weeks after pilocarpine induced SE | Not known | Increased Ca$^{2+}$ signaling in reactive astrocytes |
| Enger et al., 2015 conference proceedings, American Epilepsy Society conference | Mouse hippocampus, in vivo, unanesthetized. Chronic MTLE model of deep cortical kainate injection, imaging at 3 months after SE | GCaMP6f | Episodic spontaneous hyperactivity of reactive astrocytes within/close to the sclerotic hippocampus |
| Plata et al., 2018 | Rat, hippocampal slices, Lithium-pilocarpine | OGB-1 AM | A reduction in large size astrocytic Ca$^{2+}$ events in atrophic astrocytes |

Table 1 Key publications investigating the roles of astrocytic Ca$^{2+}$ signaling in ictogenesis and epileptogenesis.

discuss all of them would go beyond the scope of this review. One important pathway is mediated by the Inositol 1,4,5-trisphosphate (IP$_3$) receptor in the endoplasmic reticulum, of which the isoform 2 (IP$_3$R2) is thought to be the key functional IP$_3$ receptor in astrocytes (Figure 1; Sharp et al., 1999; Parri and Crunelli, 2003; Volterra and Steinhäuser, 2004; Scemes and Giaume, 2006; Foskett et al., 2007). Lack of IP$_3$R2 has been shown to abolish a large proportion of astrocytic Ca$^{2+}$ signals (Petravicz et al., 2008; Guerra-Gomes et al., 2020). In spite of the importance of IP$_3$ as a second messenger involved in astrocytic Ca$^{2+}$ dynamics, mice lacking this receptor are overtly normal (Petravicz et al., 2008). Accordingly, studies have questioned the physiological importance of IP$_3$-mediated astrocytic Ca$^{2+}$ signaling, by for instance demonstrating normal synaptic transmission and plasticity in mice devoid of IP$_3$R2 (Aguilhon et al., 2010; Nizar et al., 2013; Petravicz et al., 2014).
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FIGURE 1 | Potential roles of astrocytic Ca$^{2+}$ signaling in epilepsy. Strong astrocytic Ca$^{2+}$ signals have been shown to occur in the emergence of acute seizures (ictogenesis), that are probably triggered by neurotransmitters released by neurons. Ca$^{2+}$ increases at the onset of seizures are known to be partly mediated by release through IP$_3$R2 from the endoplasmic reticulum, even though pronounced Ca$^{2+}$ signaling is present also in mice devoid of IP$_3$R2. It is thought that intracellular Ca$^{2+}$ increases may trigger proconvulsive gliotransmitter release. In astrocytic endfeet, increased Ca$^{2+}$ signaling has been shown to correlate with ictal vasodilation. Epileptogenesis triggers a pronounced increase in mGluR5 expression, mGluR5-mediated Ca$^{2+}$ signaling, and increased glutamate uptake. An increase in astrocytic Ca$^{2+}$ signaling has been demonstrated in the days after status epilepticus, and aberrant Ca$^{2+}$ signaling at later time points in the epileptogenesis has been anecdotally reported. Increased Ca$^{2+}$ signaling could potentially cause both the release of glutamate (pro-convulsive), purines (pro-convulsive), and GABA (anti-convulsive, through Bestrophin-1 channels). In astrocytic endfoot in epileptic tissue a pronounced loss of aquaporin-4 (AQP4) and the K$^+$ inwardly rectifying channel Kir4.1 can potentially be due to Ca$^{2+}$-activated proteases causing a disassembly of the dystrophin-associated protein complex (DAPC) tethering AQP4 and Kir4.1 to perivascular endfeet. Conversely, we have demonstrated attenuated seizure activity in mice devoid of IP$_3$R2 compared to WT mice following low dose intraperitoneal kainate, suggesting a proconvulsant role of astrocytic IP$_3$R2 mediated Ca$^{2+}$ elevations (Heuser et al., 2018). However, seizure activity in this study was only collected for 1 h after initiation of seizures, encouraging further investigation of the role of IP$_3$R2 at later time points during epileptogenesis and in chronic epilepsy. Interestingly, even though a sizable amount of Ca$^{2+}$ signals were still present in the knockout mice, we found that the early activation of astrocytic Ca$^{2+}$ signals in the emergence of seizures, as discussed above, was dependent on IP$_3$R2 (Heuser et al., 2018). These two observations underscore the potential importance of IP$_3$R2 in ictogenesis.

Another pathway involved in astrocytic Ca$^{2+}$ signaling attracting increasing attention for a role in epilepsy is glial purinergic signaling (Ding et al., 2007; Wellmann et al., 2018; Alves et al., 2019; Nikolic et al., 2020). Activation of astrocytic purinergic receptors triggers intracellular Ca$^{2+}$ signals that could promote astrocytic release of gliotransmitters like glutamate or ATP, which acts on neurons and modulates excitation [reviewed in Nikolic et al. (2020)]. Importantly, Nikolic et al. (2018) provided evidence for TNFα-driven autocrine astrocyte purinergic signaling as a trigger of glutamatergic gliotransmission in a model of mesial temporal lobe epilepsy (mTLE), highlighting the complex interplay between astrocytes and microglia in epilepsy pathogenesis, discussed elsewhere (Bedner and Steinhäuser, 2019).
Most of the studies above explored the role for astrocytic Ca\(^{2+}\) signals in seizures in relation to gliotransmission, i.e., that astrocytes release transmitters that directly signal to neurons. A growing body of evidence suggests that astrocytic Ca\(^{2+}\) signals also play important roles in the control of the homeostatic functions of astrocytes. For instance they have been shown to be involved in the uptake of extracellular K\(^{+}\) through modulation of the Na\(^{+}/K\(^{+}\) ATPase, and through the breakdown of glycogen (Wang et al., 2012; Müller et al., 2014). These mechanisms remain poorly explored in the context of epilepsy but could be important downstream effects of astrocytic Ca\(^{2+}\) signaling.

**ASTROCYTIC Ca\(^{2+}\) SIGNALING AND EPILEPTOGENESIS**

Epileptogenesis refers to the gradual process by which a normal brain develops a propensity for recurrent seizure activity. A range of pathophysiological changes have been shown to occur during epileptogenesis, including inflammation, neurodegeneration, aberrant neurogenesis and dendritic plasticity, impaired blood-brain-barrier, epigenetic changes and alterations of the molecular composition and function of ion channels, receptors and transporters, and more (van Vliet et al., 2007; Vezzani et al., 2011; Steinhäuser and Seifert, 2012; Dingledine et al., 2014; Jessberger and Parent, 2015; Hauser et al., 2018; Escartin et al., 2021).

A common denominator of astrocytic pathophysiology associated with epileptogenesis is the process of reactive astrogliosis (Burda and Sofroniew, 2014; Pekny and Pekna, 2016). This is a graded response to a wide array of insults, which is a hallmark of many neurological disorders (Burda and Sofroniew, 2014; Ferlazzo et al., 2016; Glushakov et al., 2016; Pekny and Pekna, 2016; Fordington and Manford, 2020; Galovic et al., 2021).

Reactive astrocytes are characterized by morphological and molecular changes (Figure 1). Specifically they proliferate, undergo hypertrophy and increase their expression of intermediary filament proteins like glial fibrillary acid protein (GFAP) and vimentin (Yang et al., 1994; Pekny and Nilsson, 2005; Sofroniew, 2009; Cregg et al., 2014; Escartin et al., 2021).

In extremis, these changes may lead to the formation of a glial scar (Müller, 2005; Barres, 2008; Sofroniew, 2009; Burda and Sofroniew, 2014; Ferlazzo et al., 2016; Glushakov et al., 2016; Pekny and Pekna, 2016; Fordington and Manford, 2020; Galovic et al., 2021). Reactive astrogliosis can be observed in several acquired forms of epilepsy but has mostly been investigated in the context of mTLE (Wieser and ILAE Commission et al., 2021). Potentially, this is a protective mechanism to handle the elevated glutamate levels in epileptic tissue but could possibly also represent a pro-epileptic feature triggering downstream Ca\(^{2+}\) mediated gliotransmission.

The degree, development and underlying mechanisms involved in aberrant Ca\(^{2+}\) signaling in epileptogenesis are still unknown, but it is plausible that several of the physiological signaling pathways involved in astrocytic Ca\(^{2+}\) dynamics (Caudal et al., 2020), could be perturbed. A major pathway for eliciting astrocytic Ca\(^{2+}\) signals is the activation of the Gq G-protein coupled receptors (GqPCRs) and subsequent release of Ca\(^{2+}\) from the endoplasmic reticulum via IP\(_3\)R2 as discussed in “Astrocyte Ca\(^{2+}\) signaling and Ictogenesis” (Figure 1; Foskett et al., 2007). Astrocytes express several GqPCRs, of which mGluR5 has attracted most attention due to an upregulation in epileptic tissue and potential involvement in an excitatory loop comprising glutamate induced Ca\(^{2+}\) dependent glutamate release from astrocytes (Umpierre et al., 2019). While astrocytes in the adult brain are almost depleted of mGluR5 (Sun et al., 2013), the receptor is consistently expressed in chronic epilepsy models and resected tissue from patients with epilepsy (Aronica et al., 2000, 2003), and a recent study has shown that mGluR5 expression and mGluR5-dependent Ca\(^{2+}\) transients reemerge during epileptogenesis along with an increase in glutamate uptake (Umpierre et al., 2019). This reemergence of astrocytic mGluR5 could potentially be a compensatory anti-epileptic mechanism to handle the elevated glutamate levels in epileptic tissue but could possibly also represent a pro-epileptic feature triggering downstream Ca\(^{2+}\) mediated gliotransmission.

Apart from these perturbations in glutamate dynamics, it has been shown that reactive astrocytes exhibit a tonic release of GABA, presumably through Bestrophin-1 channels (Pandit et al., 2020). Bestrophin-1 channels are Ca\(^{2+}\) activated anion channels, and increased GABA release could hence be a downstream effect of increased Ca\(^{2+}\) signaling in reactive astrocytes (Lee et al., 2010). In support of this conjecture is the finding of an accumulation of GABA in reactive astrocytes in a model of mTLE (Müller et al., 2020). Potentially, this is a protective aspect of reactive astrocytes to curb epileptiform activity in this pathological tissue.

However, as mentioned in “Ictogenesis” astrocytic Ca\(^{2+}\) signaling has been suggested to be involved in homeostatic mechanisms of astrocytes. These mechanisms could be important downstream effects of astrocytic Ca\(^{2+}\) dyshomeostasis in
epileptic tissue, but these effects are so far rudimentarily investigated in epilepsy.

Loss of astrocytic gap junction coupling has been shown to occur during early epileptogenesis in experimental models of mTLE and in specimens of resected hippocampi from patients with mTLE (Bedner et al., 2015; Deshpande et al., 2017, 2020; Henning et al., 2021). It is believed that this loss of astrocytic coupling in epilepsy may perturb the ability of astrocytes to remove K+ from the extracellular space through the process of K+ spatial buffering (Nwoabi et al., 2016). Notably, astrocytic gap junctions may also allow Ca2+ signals to propagate from cell to cell, at least during pathological conditions like seizure activity (Scemes and Giaume, 2006). It is tempting to hypothesize that such propagating Ca2+ waves could play a role in neuronal synchronization and seizure generation. Potentially a loss of astrocytic gap junctions as seen in epileptic tissue, may be a compensatory mechanism to prevent intercellular spread of astrocytic Ca2+ waves. Even so, to the best of our knowledge, no direct study of astrocytic Ca2+ signaling in gap junction deficient mice has been performed.

Loss of the highly concentrated expression of key membrane channels in astrocytic endfoot processes, i.e., loss of astrocyte polarization, is another pathological hallmark, which could be a consequence of perturbed glial Ca2+ dynamics (Figure 1). For instance AQP4 and Kir4.1 are normally densely expressed in astrocytic endfeet, kept in place by the so-called dystrophin associated protein complex (DAPC) (Nagelhus et al., 1998; Enger et al., 2012), and in tissue ressects from patients with mTLE, a striking loss of this polarized expression of both AQP4 and Kir4.1 have been shown (Eid et al., 2005; Heuser et al., 2012). It is possible that prolonged epileptic activity and increased Ca2+ signaling in astrocytic endfeet, as we demonstrated in Szokol et al. (2015), activate Ca2+ dependent proteases like calpain (Nagelhus and Ottersen, 2013), that shows affinity to dystrophin and could cleave the DAPC (Figure 1; Shields et al., 2000).

Even though the evidence is indirect, it has been suggested that this loss of astrocyte endfoot polarization could contribute to epileptogenesis and hyperexcitation (Binder et al., 2012; Binder and Carson, 2013; Grunelli et al., 2015). Notably, the loss of the astrocyte endfoot Kir4.1 channels in tissue from mTLE patients (Heuser et al., 2012) is expected to cause impaired K+ handling and resultant neuronal hyperexcitation due to the role of Kir4.1 in K+ homeostasis (Borisy and Sontheimer, 1998; Hinterkeuser et al., 2000; Kivi et al., 2000; Neusch et al., 2001; Djukic et al., 2007; Bockenhauer et al., 2009; Scholl et al., 2009; Steinhäusser et al., 2012).

CONCLUSION AND FUTURE PERSPECTIVES

Here we have discussed the role of astrocyte Ca2+ signaling in ictogenesis and epileptogenesis. These terms are used to describe two different features of epilepsy, but do not necessarily imply two separate processes, as mechanisms crucial in ictogenesis could also be an integral part of epileptogenesis, or vice versa. While we often associate astrocytic dysfunction in epileptogenesis with the appearance of reactive astrogliosis (Escartin et al., 2021), the term ictogenesis seems typically to be used when studying the interplay between neurons and astrocytes independent of pre-existing tissue pathology. Therefore, we may overlook the fact that ictogenesis most often would occur in tissue that has undergone pathological transformation typical for epileptogenesis, i.e., not normal, healthy tissue. On the other hand, epileptogenesis comprises many pathological changes beyond reactive astrogliosis, like alterations in transcriptional regulation, morphological, biochemical, metabolic and physiological remodeling ultimately resulting in gain or loss of function (Escartin et al., 2021).

Astrocytic Ca2+ signals are today considered a main readout of astrocytic activity and there are reasons to believe that they play important roles in epilepsy. Evidence suggests that such signals are neither necessary nor sufficient to maintain epileptiform activity, but rather should be seen as modulators of the pathophysiological process. The literature directly investigating the role of astrocytic Ca2+ signaling in epilepsy is still sparse and at some points contradictory, and for most proposed mechanisms only a small subset of the signaling pathways involved are identified. A major challenge will be to disentangle the potentially beneficial from detrimental consequences of the different modes of astrocyte Ca2+ signaling in reactive astrogliosis. It is even probable that astrocyte Ca2+ signaling may carry different roles in the large variety of epileptic entities. To decipher the roles of astrocyte Ca2+ signaling in epilepsy, next steps should include a rigorous study of the mechanisms mentioned above in vivo in adult mice, leveraging new developments in both imaging and genetics, with the aim of identifying promising targets for future pharmacological therapy of epilepsy.

AUTHOR CONTRIBUTIONS

KH and RE reviewed the literature, conceptualized the manuscript, and wrote the manuscript. Both authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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