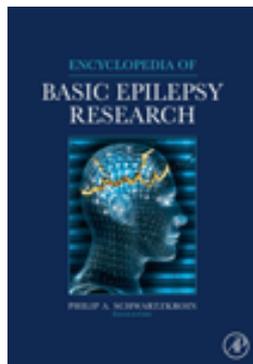


**Provided for non-commercial research and educational use.
Not for reproduction, distribution or commercial use.**

This article was originally published in the *Encyclopedia of Basic Epilepsy Research*, published by Elsevier, and the attached copy is provided by Elsevier for the author's benefit and for the benefit of the author's institution, for non-commercial research and educational use including without limitation use in instruction at your institution, sending it to specific colleagues who you know, and providing a copy to your institution's administrator.



All other uses, reproduction and distribution, including without limitation commercial reprints, selling or licensing copies or access, or posting on open internet sites, your personal or institution's website or repository, are prohibited. For exceptions, permission may be sought for such use through Elsevier's permissions site at:

<http://www.elsevier.com/locate/permissionusematerial>

Binder D K and Steinhäuser C Role of Astrocyte Dysfunction in Epilepsy. In: Philip A. Schwartzkroin, editor *Encyclopedia of Basic Epilepsy Research*, Vol 1. Oxford: Academic Press; 2009. pp. 412-417.

Further Reading

- Beach TG, Woodhurst WB, MacDonald DB, and Jones MW (1995) Reactive microglia in hippocampal sclerosis associated with human temporal lobe epilepsy. *Neuroscience Letters* 191: 27–30.
- de Lanerolle NC and Lee TS (2005) New facets of the neuropathology and molecular profile of human temporal lobe epilepsy. *Epilepsy and Behavior* 7: 190–203.
- Eid T, Thomas MJ, Spencer DD, *et al.* (2004) Loss of glutamine synthetase in the human epileptogenic hippocampus: A possible mechanism for elevated extracellular glutamate in mesial temporal lobe epilepsy. *Lancet* 363: 28–37.
- Eid T, Lee TS, Thomas MJ, *et al.* (2005) Loss of perivascular Aquaporin 4 may underlie deficient water and K⁺ homeostasis in the human epileptogenic hippocampus. *Proceedings of the National Academy of Sciences USA* 102: 1193–1198.

- Eronica E, Boer K, van Vilet EA, *et al.* (2007) Complement activation in experimental and human temporal lobe epilepsy. *Neurobiology of Disease* 26: 497–511.
- Lee TS, Mane S, Eid T, *et al.* (2007) Gene expression in temporal lobe epilepsy is consistent with increased release of glutamate by astrocytes. *Molecular Medicine* 13: 1–13.
- O'Connor ER, Sontheimer H, Spencer DD, and de Lanerolle NC (1998) Astrocytes from human hippocampal epileptogenic foci exhibit action potential like responses. *Epilepsia* 39: 347–354.
- Otis TS and Sofroniew MV (2008) Glia get excited. *Nature Neuroscience* 11: 379–380.
- Steinhauser C, Haydon PG, and de Lanerolle NC (2008) Astroglial mechanisms of epilepsy. In: Engel J Jr. and Pedley TA (eds.) *Epilepsy: A Comprehensive Textbook* vol. 2, ch. 26. Wolters Kluwer/Lippincott, Williams & Wilkins.

Role of Astrocyte Dysfunction in Epilepsy

D K Binder, University of California, Irvine, CA, USA
C Steinhäuser, University of Bonn, Bonn, Germany

© 2009 Elsevier Ltd. All rights reserved.

Introduction

Epilepsy comprises a group of brain disorders characterized by the periodic and unpredictable occurrence of seizures. Even with optimal current antiepileptic drug (AED) therapy, ~30% of patients have poor seizure control and become medically refractory. Because many AEDs act as general CNS depressants and must be taken chronically for seizure suppression, they often have marked inhibitory effects on cognition.

Thus, more specific AEDs that target cellular and molecular abnormalities responsible for epilepsy but not globally affect cerebral function need to be developed. In this regard, recent developments in understanding glial (especially astrocytic) changes in epilepsy can potentially provide novel therapeutic targets. For simplicity, in this article we refer to different types of cells with astroglial properties as 'astrocytes.'

Background and Results

Glial Morphological Changes in Temporal Lobe Epilepsy

Alterations in astrocytic properties have been best described in the specific case of human temporal lobe epilepsy. The most common pathology found in patients with medically-intractable temporal lobe epilepsy is hippocampal sclerosis, more generally termed mesial temporal sclerosis. Mesial temporal sclerosis is characterized by

neuronal cell loss in specific hippocampal areas, gliosis, microvascular proliferation, and synaptic reorganization. One striking hallmark of sclerotic hippocampus is that while there is a specific pattern of neuronal loss, there is also 'reactive gliosis' with hypertrophic glial cells exhibiting prominent Glial Fibrillary Acidic Protein (GFAP) staining and long, thick processes. Most of the changes in astrocytic channels and transporters described later have been discovered in sclerotic hippocampi from temporal lobe epilepsy patients. However, the cellular and molecular processes leading to astrocytic changes during epileptogenesis are not yet understood.

Glial Glutamate Receptors and Transporters in Temporal Lobe Epilepsy

Dysfunction of glutamate transport and synthesis

Glutamate transporters are expressed by several CNS cell types, but astrocytes are primarily responsible for glutamate uptake. The astroglial transporter GLT-1 is responsible for the clearance of bulk extracellular glutamate in the CNS, and increased extracellular levels of glutamate have been found in epileptogenic foci. GLT-1 knockout in mice caused spontaneous seizures and hippocampal pathology resembling alterations in temporal lobe epilepsy patients with mesial temporal sclerosis. Several human studies have supported the hypothesis that reduced or dysfunctional glial glutamate transporters in the hippocampus may trigger spontaneous seizures in patients with mesial temporal sclerosis ([Table 1](#)), yet the underlying mechanisms are unclear.

Table 1 Involvement of astroglial membrane channels, transporters, and receptors in specific epilepsy syndromes

Epilepsy syndrome	Astroglial molecule	Effect	Species	Methods
Temporal lobe epilepsy	GLT-1	No change	Human	IHC, WB, ISH
Temporal lobe epilepsy	GLAST	No change		
Temporal lobe epilepsy	GLT-1	↓	Human	IHC
Temporal lobe epilepsy	GLAST	No change		
Temporal lobe epilepsy	GLT-1	↓	Human	IHC, ISH
Temporal lobe epilepsy	GLAST	↓		
Temporal lobe epilepsy	GLT-1	No change	Human	IHC, WB,
Temporal lobe epilepsy	(Glutamine synthetase)	(↓)		enzyme activity
Temporal lobe epilepsy	GluR1 ('flip' variant)	↑	Human	PC, pharmacology (CTZ, PEPA), single-cell rtPCR, RA
Temporal lobe epilepsy	mGluR2/3	↑	Human	IHC
	mGluR5	↑		
	mGluR8	↑		
Temporal lobe epilepsy	Kir channel	↓	Human	PC
Temporal lobe epilepsy	Kir channel	↓	Human	ISM, Ba ²⁺
		↓	Rat (pilocarpine)	
Temporal lobe epilepsy	Kir channel	↓	Human	PC, Ba ²⁺ , single-cell rtPCR
Temporal lobe epilepsy	AQP4	↑ overall	Human	IHC, rtPCR, gene chip, EM
		↓ perivascular		
Focal cortical dysplasia	mGluR2/3	↑	Human	IHC
	mGluR5	↑		
Tuberous sclerosis	GLAST	↓	<i>Tsc1</i> ^{GFAP} CKO mouse	WB, PC
	GLT-1	↓		
Tuberous sclerosis	Kir channel	↓	<i>Tsc1</i> ^{GFAP} CKO mouse	PC, WB, Ba ²⁺ , mRNA analysis
Tumor-associated epilepsy	GluR2	↓ Q/R editing	Human glioma	rtPCR, sequencing
Tumor-associated epilepsy	GLT-1	↓	Human glioma	IHC
Tumor-associated epilepsy	GLAST	Mislocalized		
Tumor-associated epilepsy	Kir channel	↓	Human glioma	PC
		Mislocalized		WB, IHC
Posttraumatic epilepsy	Kir and Kv channels	↓	Rat (fluid-percussion injury)	PC, ISM
Posttraumatic epilepsy	GLT-1	↓	Rat (ferrous chloride)	WB
	GLAST	No change		

CTZ, cyclothiazide; EM, electron microscopy; IHC, immunohistochemistry; ISH, in situ hybridization; ISM, ion-sensitive microelectrodes; PC, patch clamp; PEPA, 4-[2-(phenylsulfonylamino)ethylthio]-2,6-difluoro-phenoxyacetamide; RA, restriction analysis; rtPCR, reverse transcriptase polymerase chain reaction; WB, Western blot. Modified from Binder DK and Steinhäuser C (2006) Functional changes in astroglial cells in epilepsy. *Glia* 54: 358–368.

Alternatively, alterations in glutamate metabolism may be important. de Lanerolle's group has found reduced glutamine synthetase, an enzyme in astrocytes that converts glutamate into glutamine, in sclerotic rather than in non-sclerotic hippocampus of temporal lobe epilepsy patients (Table 1). Downregulation of glutamine synthetase would slow down glutamate–glutamine cycling and accumulation of the transmitter in astrocytes and in the extracellular space. This condition would provide a metabolic mechanism for astrocyte-dependent hyperexcitability.

Alterations of ionotropic glutamate receptors

A few studies have addressed the potential involvement of ionotropic glutamate receptors in seizure generation. Astrocytes abundantly express receptors of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype composed of the subunits GluR1 to

GluR4. Combined functional and single-cell transcript analyses revealed that enhanced expression of GluR1 flip variants accounts for the prolonged receptor responses observed in hippocampal astrocytes of epilepsy patients with mesial temporal sclerosis (Table 1). Prolonged opening of receptor will promote influx of Ca²⁺ and Na⁺ ions. Steinhäuser's group has shown that enhanced intracellular Na⁺ blocks inwardly rectifying astroglial K⁺ (Kir) channels, further strengthening depolarization and reducing the K⁺ buffering capacity of astrocytes, and thus contributing to hyperexcitability.

Metabotropic glutamate receptors and astroglial Ca²⁺ signalling in epilepsy

mGluR3 and mGluR5 are the predominant metabotropic glutamate receptor subtypes expressed by glial cells. Activation of these receptors affects cAMP accumulation and leads to an increase in intracellular Ca²⁺. Group II

mGluRs (mGluR 2, 3) have been shown to be coupled to cAMP levels in cultured astrocytes. mGluR-triggered rise in Ca^{2+} may cause oscillations and initiate Ca^{2+} wave propagation within the astrocyte network, activate Ca^{2+} -dependent ion channels, and induce glutamate release from astrocytes. In experimental epilepsy, reactive astrocytes of the hippocampus persistently upregulate mGluR3, mGluR5, and mGluR8 protein. Electron microscopic and immunohistochemical inspection of hippocampal tissue from temporal lobe epilepsy patients revealed expression of mGluR2/3, mGluR4, mGluR5, and mGluR8 in reactive astrocytes, suggesting an involvement of these receptors in gliosis. Upregulation of astroglial mGluR2/3 and mGluR5 was also observed in epileptic specimens from patients with focal cortical dysplasia (Table 1). However, the functional role of glial mGluR upregulation in epilepsy is not yet clear.

Astrocytic Glutamate Release in Epilepsy

Astrocytes are capable of releasing glutamate through a Ca^{2+} -dependent process, which could be involved in seizure generation. In chemically-induced, acute epilepsy models, it was recently reported that astrocytes contribute to the generation of synchronized epileptiform activity. In these studies, epileptiform discharges were provoked through the application of 4-aminopyridine, GABA_A receptor antagonists, or bath solutions containing low concentrations of divalent cations. It appeared that astrocytic increase in $[\text{Ca}^{2+}]_i$ is sufficient to stimulate release of glutamate from glial cells, which was critical for the generation of paroxysmal depolarization shifts (PDSs), a hallmark of epileptiform activity. In addition, *in vivo* imaging showed that some antiepileptic drugs suppressed astrocytic Ca^{2+} -signalling. An important caveat to these studies is that human epilepsy is associated with significant morphological alterations that are absent in acute models that have been studied.

Astrocyte Potassium and Water Channels

Since both extracellular K^+ concentration and osmolarity have been shown to markedly modulate neural excitability, it is plausible that changes in astrocytic K^+ or water channels could contribute to hyperexcitability in epilepsy. Indeed, recent studies have found changes in astroglial Kir channels and AQP4 water channels in temporal lobe epilepsy specimens.

K^+ channels

During neuronal hyperactivity, extracellular $[\text{K}^+]$ may increase from ~ 3 mM to a ceiling of 10–12 mM; and K^+ released by active neurons is thought to be primarily

taken up by glial cells. Any impairment of glial K^+ uptake would be expected to be proconvulsant. In the hippocampus, millimolar and even submillimolar increases in extracellular K^+ concentration enhance epileptiform activity. High- K^+ also reliably induces epileptiform activity in hippocampal slices from human patients with intractable temporal lobe epilepsy and hippocampal sclerosis.

A primary mechanism for K^+ reuptake is thought to be via inwardly rectifying glial K^+ channels (Kir channels). Glial Kir channels may contribute to K^+ reuptake and spatial K^+ buffering, which has been most clearly demonstrated in the retina. Although multiple subfamilies of Kir channels exist (Kir1–Kir7) differing in tissue distribution and functional properties, the expression of Kir4.1 in brain astrocytes has been investigated most thoroughly. Pharmacological or genetic inactivation of Kir4.1 leads to impairment of extracellular K^+ regulation. However, members of the strongly rectifying Kir2 family may also contribute to astroglial K^+ buffering.

Downregulation of astroglial Kir channels has been found in the injured or diseased CNS. Kir currents are reduced following injury-induced reactive gliosis *in vitro*, entorhinal cortex lesion, freeze lesion-induced cortical dysplasia, and traumatic and ischemic brain injury. In addition, several studies have indicated downregulation of Kir currents in specimens from patients with temporal lobe epilepsy. Using ion-sensitive microelectrodes, U. Heinemann's group compared glial Ba^{2+} -sensitive K^+ uptake in the CA1 region of hippocampal slices obtained from patients with or without mesial temporal sclerosis. Ba^{2+} , a blocker of Kir channels, augmented stimulus-evoked K^+ elevation in non-sclerotic but not in sclerotic specimens, suggesting an impairment in K^+ buffering in sclerotic tissue. Direct evidence for downregulation of Kir currents in the sclerotic CA1 region of hippocampus came from a comparative patch-clamp study in which a reduction in astroglial Kir currents was observed in sclerotic hippocampi compared with that in non-sclerotic hippocampi (Table 1). These data indicate that dysfunction of astroglial Kir channels could underlie impaired K^+ buffering and contribute to hyperexcitability in epileptic tissue. When and how this dysfunction develops during epileptogenesis is not yet clear.

Water channels

Alterations in astroglial water regulation could also highly affect excitability. Brain tissue excitability is extremely sensitive to osmolarity and the size of the extracellular space (ECS). Decreasing ECS volume produces hyperexcitability and enhanced epileptiform activity; conversely, increasing ECS volume with hyperosmolar medium attenuates epileptiform activity. These experimental data parallel extensive clinical experience indicating that hypo-osmolar states such as hyponatremia lower seizure

threshold while hyperosmolar states elevate seizure threshold.

The aquaporins (AQPs) are a family of membrane proteins that function as 'water channels' in many cell types and tissues in which fluid transport is crucial. Aquaporin-4 (AQP4) is expressed ubiquitously by glial cells, especially at specialized membrane domains including astroglial end-feet in contact with blood vessels and astrocyte membranes that ensheath glutamatergic synapses. Activity-induced radial water fluxes in neocortex have been suggested to occur as a result of water movement via aquaporin channels in response to physiological activity. Mice deficient in AQP4 have shown marked decrease in accumulation of brain water (cerebral edema) following water intoxication and focal cerebral ischemia and impaired clearance of brain water in models of vasogenic edema, suggesting a functional role for AQP4 in brain water transport. Similarly, mice deficient in dystrophin or α -syntrophin, in which there is mislocalization of the AQP4 protein, also show attenuated cerebral edema.

Alteration in the expression and subcellular localization of AQP4 has been described in sclerotic hippocampi obtained from patients with mesial temporal sclerosis. One study using immunohistochemistry, rt-PCR, and gene chip analysis reported an overall increase in AQP4 expression in sclerotic hippocampi. However, using quantitative immunogold electron microscopy, the same group found that there was mislocalization of AQP4 in the human epileptic hippocampus, with reduction in perivascular membrane expression (Table 1). The authors hypothesized that the loss of perivascular AQP4 perturbs water flux, impairs K^+ buffering, and results in an increased propensity for seizures.

Several lines of evidence support the hypothesis that AQP4 and Kir4.1 may act in concert in K^+ and H_2O regulation. First, reuptake of K^+ into glial cells could be AQP4-dependent, as water influx coupled to K^+ influx is thought to underlie activity-induced glial cell swelling. Second, studies in the retina have demonstrated subcellular co-localization of AQP4 and Kir4.1 via both electron microscopic and co-immunoprecipitation analyses. Third, Kir4.1^{-/-} mice, like AQP4^{-/-} mice, have impaired retinal and cochlear physiology presumably due to altered K^+ metabolism. Fourth, AQP4^{-/-} mice have remarkably slowed K^+ reuptake in models of seizure and spreading depression in vivo associated with a near-threefold increase in seizure duration. Fifth, afferent stimulation of hippocampal slices from α -syntrophin-deficient mice demonstrates a deficit in extracellular K^+ clearance. These data are consistent with the idea that AQP4 and Kir4.1 participate in clearance of K^+ following neural activity. However, further studies are required to clarify the expression and functional interaction of AQP4 and Kir4.1 in the brain and their changes during epileptogenesis.

Astrocyte Dysfunction Involved in other Epilepsy Syndromes

Tuberous sclerosis

Tuberous sclerosis (TS) is a multisystem genetic disorder resulting from autosomal dominant mutations of either *TSC1* or *TSC2* genes. The *TSC1* gene encodes the protein hamartin and *TSC2* encodes tuberin, which are thought to be regulators of cell signalling and growth. Epilepsy occurs in 80–90% of cases of TS, frequently involves multiple seizure types and is often medically refractory. Cortical tubers represent the pathologic substrate of TS, and microscopically consist of a specific type of dysplastic lesion with astrocytosis and abnormal giant cells. Although this suggests that astrocytes are involved in the pathologic lesion, in itself this is not the evidence for a causative role of astrocytes in TS epileptogenesis. However, recent evidence using astrocyte-specific *TSC1* conditional knockout mice has provided insight into a potential role of astrocytes in the etiology of TS. These mice, which have conditional inactivation of the *TSC1* gene in GFAP-expressing cells (*Tsc1*^{GFAP}CKO mice), develop severe spontaneous seizures by 2 months of age and die prematurely. Intriguingly, the time point of onset of spontaneous seizures in these mice is concordant with increased astroglial proliferation. Furthermore, two functions of astrocytes – glutamate and K^+ reuptake – are impaired in these mice. These mice display reduced expression of the astrocyte glutamate transporters GLT1 and GLAST. In addition, recent evidence indicates that astrocytes from *Tsc1*^{GFAP}CKO mice exhibit reduced Kir channel activity, and hippocampal slices from these mice demonstrated increased sensitivity to K^+ -induced epileptiform activity (Table 1). Together, these studies demonstrate that in this model, changes in glial properties may be a direct cause of epileptogenesis.

Tumor-associated epilepsy

Tumor-associated epilepsy is an important clinical problem, seen in approximately one-third of cases. Surgical removal of tumors usually results in seizure control, but many tumors cannot safely be resected, and tumor-associated seizures are often resistant to anticonvulsant therapy. Classic epilepsy-associated brain tumors include astrocytoma, oligodendroglioma, ganglioglioma, dysembryoplastic neuroepithelial tumor, and pleomorphic xanthoastrocytoma. Microdialysis studies of gliomas have revealed reduced glutamate in the tumor compared to peri-tumoral tissue. A 'glutamate hypothesis' of tumor-associated epilepsy has been advanced which suggests that tumors excite surrounding tissue by glutamate overstimulation. Two lines of evidence are relevant to this hypothesis. First, the glutamate receptor subunit GluR2 has been found to be under-represented at the Q/R site in gliomas, which would

increase AMPA receptor Ca^{2+} permeability and potentially result in increased glutamate release by glioma cells (Table 1). Second, glioma cells release larger than normal amounts of glutamate *in vitro*. The release of glutamate from glioma cells is accompanied by a marked deficit in Na^+ -dependent glutamate uptake, reduced expression of astrocytic glutamate transporters, and upregulation of cystine-glutamate exchange (Table 1). Hence, glioma cell glutamate release at the margins of the tumor may initiate seizures in peritumoral neurons. A distinct potential mechanism underlying tumor-associated epilepsy is altered K^+ homeostasis. In support of this hypothesis, both reduced Kir currents and mislocalization of Kir4.1 channels have been found in malignant astrocytes (Table 1).

Posttraumatic epilepsy

Posttraumatic epilepsy refers to a recurrent seizure disorder whose cause is believed to be traumatic brain injury. It is a common and important form of epilepsy, and develops in a variable proportion of traumatic brain injury survivors depending on the severity of the injury and the time after injury. Anticonvulsant prophylaxis is ineffective at preventing the occurrence of late seizures. Weight-drop and fluid-percussion injury animal models of posttraumatic epilepsy have demonstrated characteristic structural and functional changes in the hippocampus, such as death of dentate hilar neurons and mossy fiber sprouting. Recently, studies have also implicated altered astrocyte function in posttraumatic epilepsy models. Recordings from glial cells in hippocampal slices 2 days after fluid-percussion injury demonstrated reduction in transient outward and inward K^+ currents (Table 1), and antidromic stimulation of CA3 led to abnormal extracellular K^+ accumulation in posttraumatic slices compared to controls. This was accompanied by the appearance of electrical afterdischarges in CA3. Thus, this study suggests impaired K^+ homeostasis in posttraumatic hippocampal glia. Another study demonstrated reduction in expression of the astrocyte glutamate transporter GLT1 in a posttraumatic epilepsy model induced by intracortical ferrous chloride injection (Table 1), suggesting impaired glutamate transport. Further studies of the role of glial cells in posttraumatic epilepsy appear warranted now that reliable posttraumatic epilepsy animal models have been developed.

Perspectives and Future Directions

Astrocytes undergo cellular and molecular changes in epilepsy, including alteration in glutamate transporters and receptors as well as Kir channels and water channels. So far, most of these changes have been demonstrated in

sclerotic hippocampi from patients with temporal lobe epilepsy or animal models resembling this particular human condition. However, the various functions of astrocytes in modulation of synaptic transmission and glutamate, K^+ and H_2O regulation suggest that astrocyte dysfunction could also be part of the pathophysiology of other forms of epilepsy.

One important recent development is the recognition of structural and functional heterogeneity of cells with astroglial properties. It is clear that a subset of hippocampal astroglial cells ('classical' astrocytes or GluT cells) expresses glutamate transporters and not ionotropic glutamate receptors and another (NG2 glia or GluR cells) expresses ionotropic glutamate receptors but not glutamate transporters. However, the lineage relationship of NG2 glia/GluR cells and the relative roles of *bona fide* astrocytes versus NG2 glia/GluR cells in epilepsy still remain unclear. In addition, the functional roles of ionotropic glutamate receptors, Kir and AQP4 channels in these subsets of glial cells in the hippocampus are not yet understood. Hippocampal NG2 glia/GluR cells lack gap junctional coupling but receive direct synaptic input from GABAergic and glutamatergic neurons. Gap junctions may also regulate excitability, although available data are inconsistent regarding the impact of altered connexin expression on epileptogenesis. The availability of mice with genetically uncoupled astrocytes will allow examination of this question, by separating the effects produced by alterations of neuronal versus glial gap junctions. It will be important in future studies to examine the cellular and molecular properties of subsets of hippocampal glial cells in human epileptic tissue and unravel the course of their functional alterations during epileptogenesis in appropriate animal models.

Another recent focus in astrocyte biology that may become important for epilepsy research is the 'gliovascular junction.' Microvascular proliferation in the sclerotic hippocampus was noted as early as 1899, but the role of the vasculature and the blood-brain barrier in epilepsy is not yet clear. The intimate relationship between astroglial endfeet ensheathing blood vessels, the targeted expression of AQP4 and Kir4.1 on astroglial endfeet, and the role of astrocytes in blood-brain barrier permeability and control of microcirculation have only recently been appreciated. Local pathological alterations in the gliovascular junction could perturb blood flow, K^+ and H_2O regulation and constitute an important mechanism in the generation of hyperexcitability. Indeed, a recent study suggests that transient opening of the blood-brain barrier is actually sufficient for focal epileptogenesis. The cellular and molecular roles of the gliovascular junction in metabolic homeostasis and changes during epileptogenesis are only beginning to be explored.

In conclusion, the exact changes taking place in astroglial functioning during epilepsy are still poorly understood. The term 'reactive gliosis' is too descriptive and should be replaced by careful morphological, biochemical, and electrophysiological studies of identified glial cell subtypes in human tissue and animal models. In addition to changes in preexisting glial cell populations, newly-generated glial cells with distinct properties may migrate into the hippocampus and contribute to enhanced seizure susceptibility. The available data likely represent only the 'tip of the iceberg' in terms of the functional role of astroglial cells in epilepsy. In view of the many physiologic functions of astrocytes that have been elucidated within the past decade, it can be expected that the next few years of research will yield evidence of similar important roles for glial cells in pathophysiology. Further study of astrocyte alterations in epilepsy should lead to the identification of novel molecular targets that might open new avenues for the development of alternative antiepileptic therapies.

Acknowledgements

D.K.B. is supported by a American Epilepsy Society/Milken Family Foundation Early Career Physician Scientist Award. C.S. is supported by grants from the Deutsche Forschungsgemeinschaft (SFB/TR3; SPP1172). We apologize to all those whose work could not be discussed because of space constraints.

See also: **Glia/Astrocytes:** Astrocytic Regulation of Neuronal Excitability; Glial Modulation of Excitability via Glutamate and GABA Transporters; Glial-Mediated Mechanisms of Epileptogenesis in Tuberous Sclerosis; Peritumoral Epilepsy; Properties of Glia in Epileptic Brain; Tumor-Induced Epilepsy and Epileptogenic Potential of Brain Tumor Treatment; **Neurotrophic Factors:** Role of BDNF in Animal Models of Epilepsy; **Non-Synaptic Mechanisms:** Changes in Extracellular Ion Composition; Changes in Extracellular Space as a Modulator of Excitability and Epileptogenicity; Modulation of Neuronal Excitability by Changes in Extracellular Ion Composition; Role of Aquaporins in Non-Synaptic Mechanisms of Epilepsy; **Transporters:** Function of Cell-Surface Glutamate Transporters in the Brain: An Important Role for Development and Preventing Seizures.

Further Reading

- Binder DK and Steinhäuser C (2006) Functional changes in astroglial cells in epilepsy. *Glia* 54: 358–368.
- During MJ and Spencer DD (1993) Extracellular hippocampal glutamate and spontaneous seizure in the conscious human brain. *Lancet* 341: 1607–1610.
- Eid T, Thomas MJ, Spencer DD, Runden-Pran E, Lai JC, Malthankar GV, Kim JH, Danbolt NC, Ottersen OP, and de Lanerolle NC (2004) Loss of glutamine synthetase in the human epileptogenic hippocampus: Possible mechanism for raised extracellular glutamate in mesial temporal lobe epilepsy. *Lancet* 363: 28–37.
- Hinterkeuser S, Schröder W, Hager G, Seifert G, Blümcke I, Elger CE, Schramm J, and Steinhäuser C (2000) Astrocytes in the hippocampus of patients with temporal lobe epilepsy display changes in potassium conductances. *The European Journal of Neuroscience* 12: 2087–2096.
- Jansen LA, Uhlmann EJ, Crino PB, Gutmann DH, and Wong M (2005) Epileptogenesis and reduced inward rectifier potassium current in tuberous sclerosis complex-1-deficient astrocytes. *Epilepsia* 46: 1871–1880.
- Kivi A, Lehmann TN, Kovacs R, Eilers A, Jauch R, Meencke HJ, von Deimling A, Heinemann U, and Gabriel S (2000) Effects of barium on stimulus-induced rises of $[K^+]_o$ in human epileptic non-sclerotic and sclerotic hippocampal area CA1. *The European Journal of Neuroscience* 12: 2039–2048.
- Matthias K, Kirchhoff F, Seifert G, Hüttmann K, Matyash M, Kettenmann H, and Steinhäuser C (2003) Segregated expression of AMPA-type glutamate receptors and glutamate transporters defines distinct astrocyte populations in the mouse hippocampus. *Journal of Neuroscience* 23: 1750–1758.
- Schwartzkroin PA, Baraban SC, and Hochman DW (1998) Osmolarity, ionic flux, and changes in brain excitability. *Epilepsy Research* 32: 275–285.
- Seiffert E, Dreier JP, Ivens S, Bechmann I, Tomkins O, Heinemann U, and Friedman A (2004) Lasting blood-brain barrier disruption induces epileptic focus in the rat somatosensory cortex. *Journal of Neuroscience* 24: 7829–7836.
- Seifert G, Hüttmann K, Schramm J, and Steinhäuser C (2004) Enhanced relative expression of glutamate receptor 1 flip AMPA receptor subunits in hippocampal astrocytes of epilepsy patients with Ammon's horn sclerosis. *Journal of Neuroscience* 24: 1996–2003.
- Steinhäuser C and Seifert G (2002) Glial membrane channels and receptors in epilepsy: Impact for generation and spread of seizure activity. *European Journal of Pharmacology* 447: 227–237.
- Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, Oberheim N, Lou N, Wang X, Zielke HR, Kang J, and Nedergaard M (2005) An astrocytic basis of epilepsy. *Nature Medicine* 11: 973–981.
- Volterra A and Steinhäuser C (2004) Glial modulation of synaptic transmission in the hippocampus. *Glia* 47: 249–257.
- Wallraff A, Kohling R, Heinemann U, Theis M, Willecke K, and Steinhäuser C (2006) The impact of astrocytic gap junctional coupling on potassium buffering in the hippocampus. *Journal of Neuroscience* 26: 5438–5447.
- Ye ZC, Rothstein JD, and Sontheimer H (1999) Compromised glutamate transport in human glioma cells: Reduction-mislocalization of sodium-dependent glutamate transporters and enhanced activity of cystine-glutamate exchange. *Journal of Neuroscience* 19: 10767–10777.