Role of Astrocyte Dysfunction in Epilepsy☆

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Introduction

Epilepsy comprises a group of disorders of the brain 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. As many AEDs act as general CNS depressants and must be taken chronically for seizure suppression, they often have marked inhibitory effects on cognition.

Thus, there is a need for the development of more specific AEDs that may target cellular and molecular abnormalities responsible for epileptogenesis but not globally affect cerebral function. In this regard, recent developments in the understanding of 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".

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 in patients 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 the sclerotic hippocampus is that while there is a specific pattern of neuronal loss, there is also "reactive gliosis" with hypertrophic glial cells exhibiting prominent GFAP staining and long, thick processes. Most of the changes in astrocytic channels and transporters described below 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 bulk of extracellular glutamate clearance in the CNS, and increased

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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, yet the underlying mechanisms are unclear.

Alternatively, alterations in glutamate metabolism may be important. Eid et al. found reduced glutamine synthetase in the sclerotic versus non-sclerotic hippocampus of temporal lobe epilepsy patients. Downregulation of glutamine synthetase would cause a slowing of glutamate-glutamine cycling and accumulation of the transmitter in astrocytes and in the extracellular space. This would provide a metabolic mechanism for astrocyte-dependent hyperexcitability (Table 1).

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 AMPA subtype composed of the subunits GluR1 to GluR4. Combined functional and single-cell transcript analyses have 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 receptor opening will promote influx of Ca^{2+} and Na^{+} ions, and the latter block astroglial Kir channels which will further strengthen depolarization and reduce the K^{+} buffering capacity of astrocytes, thus contributing to hyperexcitability.

Metabotropic Glutamate Receptors and Astroglial Ca^{2+} 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 Ca^{2+}, respectively. Group II mGluRs (mGluR 2, 3) have been shown to be coupled to cAMP levels in cultured astrocytes. A mGluR-triggered rise in Ca^{2+} may oscillate 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 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 $[Ca^{2+}]_i$ 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.

Astrocyte Potassium and Water Channels

Since both extracellular K^{+}concentration and osmolarity have been shown to dramatically modulate neural excitability, it is plausible that changes in astrocytic K^{+} or water channels could contribute to hyperexcitability in epilepsy. Indeed, several studies have found changes in astroglial Kir channels and AQP4 water channels in temporal lobe epilepsy specimens (Table 1).

K^{+} Channels

During neuronal hyperactivity, extracellular $[K^{+}]$ 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 $[K^{+}]$ powerfully enhance epileptiform activity. High-$[K^{+}]$ also reliably induces epileptiform activity in hippocampal slices from patients with intractable temporal lobe epilepsy and hippocampal sclerosis.

A primary mechanism for K^{+} reuptake is thought to be via glial inwardly rectifying 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. While multiple subfamilies of Kir channels exist (Kir1-Kir7) differing in tissue distribution and functional properties, in brain astrocytes the

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

Epilepsy syndrome	*Astroglial molecule*	*Effect*	*Species*	*Methods*
Temporal lobe epilepsy	Gap junction	↓	Human, Mouse	PC, pharmacology, IHC, K^+ measurement EEG analysis
Temporal lobe epilepsy	GLT-1 GLAST	No change No change	Human	IHC, WB, ISH
Temporal lobe epilepsy	GLT-1 GLAST	↓ No change	Human	IHC
Temporal lobe epilepsy	GLT-1 GLAST	↓ ↓	Human	IHC, ISH
Temporal lobe epilepsy	GLT-1 (glutamine synthetase)	No change (↓)	Human	IHC, WB, enzyme activity
Temporal lobe epilepsy	GluR1 ("flip" variant)	↑	Human	PC, pharmacology (CTZ, PEPA), single-cell rtPCR, RA
Temporal lobe epilepsy	mGluR2/3 mGluR5 mGluR8	↑ ↑ ↑	Human	IHC
Temporal lobe epilepsy	Kir channel	↓	Human	PC
Temporal lobe epilepsy	Kir channel	↓ ↓	Human Rat (pilocarpine)	ISM, Ba^{2+}
Temporal lobe epilepsy	Kir channel	↓	Human	PC, Ba^{2+}, single-cell rtPCR
Temporal lobe epilepsy	AQP4	↑ overall ↓ perivascular	Human	IHC, rtPCR, gene chip, EM
Focal cortical dysplasia	mGluR2/3 mGluR5	↑ ↑	Human	IHC
Tuberous sclerosis	GLAST GLT-1	↓ ↓	*Tsc1*^{GFAP}CKO mouse	WB, PC
Tuberous sclerosis	Kir channel	↓	*Tsc1*^{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 GLAST	↓ Mislocalized	Human glioma	IHC
Tumor-associated epilepsy	Kir channel	↓ Mislocalized	Human glioma	PC WB, IHC
Post-traumatic epilepsy	Kir and Kv channels	↓	Rat (fluid-percussion injury)	PC, ISM
Post-traumatic epilepsy	GLT-1 GLAST	↓ No change	Rat (ferrous chloride)	WB

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.

expression of Kir4.1 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, 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 our comparative patch-clamp study in which a reduction in astroglial Kir currents was observed in sclerotic compared to non-sclerotic hippocampi. These data indicate that dysfunction of astroglial Kir channels could underlie impaired K^+ buffering and contribute to hyperexcitability in epileptic tissue (Table 1). When and how this dysfunction develops during epileptogenesis is not yet clear.

Water Channels

Alterations in astroglial water regulation could also powerfully affect excitability. Brain tissue excitability is exquisitely 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 endfeet in contact with blood vessels and astrocyte membranes that ensheath glutamatergic synapses. Activity-induced radial water fluxes in neocortex have been demonstrated that could be due to water movement via aquaporin channels in response to physiological activity. Mice deficient in AQP4 have markedly decreased 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 demonstrate 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 demonstrated 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. 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, K^+ reuptake 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. Reduction and mislocalization of AQP4 during early epileptogenesis has been recently demonstrated by two laboratories, indicating a potential contribution of AQP4 dysregulation in epileptogenesis (Table 1).

Astrocyte Gap Junction Coupling

Electrical coupling between cells is accomplished through the formation of gap junctions. Composed of connexin proteins, gap junctions are found on multiple cell types and connexin expression is cell type-specific. All gap junctions play a role in cellular communication, but astrocytic gap junctions are thought to be key for K^+ and glutamate redistribution, synaptic strength regulation, and memory formation. Both human tissue studies and animal models of epilepsy have shown considerable changes in connexin expression after seizure activity. Electrophysiological studies have implicated gap junctions in the generation of very fast oscillations that precede seizures. Knockout and gap junction inhibitors studies have demonstrated potential anticonvulsant effects, although these results are mixed and suffer from lack of specificity of many of the currently available gap junction inhibitors.

In a recent study we have examined functional properties of astrocytes in epilepsy tissue specimens from patients with mesial temporal lobe epilepsy with ($n = 75$) and without ($n = 44$) sclerosis. We found that in patients with hippocampal sclerosis, there is a complete absence of bona fide astrocytes and gap junctional coupling (Table 1). In contrast, coupled astrocytes were abundant in non-sclerotic human hippocampi.

In the same study, we have examined astrocytic gap junctional coupling in an animal model of temporal lobe epilepsy. In this unilateral intracortical kainic acid model of epilepsy, mice exhibited decreased astrocytic coupling already 4 h post injection and completely lacked coupling three and 6 months after status epilepticus in the sclerotic hippocampus (Table 1). In the contralateral, non-sclerotic hippocampus, however, coupling remained intact. Importantly, decreased astrocyte coupling preceded apoptotic neuronal death and the onset of spontaneous seizures, and impaired K^+ clearance. We assume that pro-inflammatory cytokines induced the uncoupling of hippocampal astrocytes in vivo, because incubation of acute slices in cytokines had an inhibitory effect on astrocytic coupling. To further test the hypothesis that inflammation may contribute to the pathogenesis of seizures and epilepsy, lipopolysaccharide was injected into mice. Five days post injection, animals exhibited reduced coupling, and the uncoupling effect of lipopolysaccharide could be fully prevented with the anti-inflammatory and antiepileptic drug levetiracetam. In addition, uncoupling was prevented in Toll-like receptor 4 (TLR4) knockout mice. Taken together, our data suggest that inflammation induces rapid uncoupling of astrocytes and uncoupling of astrocytes may contribute or even cause 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 the TSC1 or TSC2 genes. The TSC1 gene encodes the protein hamartin and TSC2 encodes tuberin, which are thought to be regulators of cell signaling

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. While this suggests that astrocytes are involved in the pathologic lesion, in itself this is not evidence for a causative role of astrocytes in TS epileptogenesis. However, experiments with 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 this model. These mice display reduced expression of the astrocyte glutamate transporters GLT1 and GLAST. In addition, 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 underedited 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. 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). A recent study in a validated mouse glioma model indicates a significant contribution of GABAergic disinhibition and impaired KCC2 cotransporter activity to excitability in peritumoral neurons.

Post-traumatic Epilepsy

Post-traumatic epilepsy refers to a recurrent seizure disorder whose cause is believed to be traumatic brain injury. It is a common 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 post-traumatic epilepsy have demonstrated characteristic structural and functional changes in the hippocampus, such as death of dentate hilar neurons and mossy fiber sprouting. Several studies have also implicated altered astrocyte function in post-traumatic epilepsy models. Recordings from glial cells in hippocampal slices 2 days after fluid-percussion injury demonstrated reduction in transient outward and inward K^+ currents, and antidromic stimulation of CA3 led to abnormal extracellular K^+ accumulation in post-traumatic 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 post-traumatic epilepsy model induced by intracortical ferrous chloride injection, suggesting impaired glutamate transport (Table 1). Further studies of the role of glial cells in post-traumatic epilepsy appear warranted now that reliable post-traumatic 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, gap junctions and water channels (Table 1). 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 astrocytes. For example, in some brain regions (eg, the hippocampus) astrocytes lack ionotropic ATP and glutamate receptors while in others (eg, the neocortex) they express them. A similar diversity exists with respect to panglial coupling, because in some regions (eg, the thalamus) astrocytes abundantly form gap junctions with oligodendrocytes but in other areas astrocyte-oligodendrocyte

coupling is almost lacking (eg, in the hippocampus). Moreover, a fourth type of glial cells has been identified, termed NG2 glia, which express a plethora of ion channels and receptors and receive direct synaptic input from neurons. Neither the functional diversity of astrocytes nor the impact of neuron-NG2 glia synapses in the normal or diseased brain are yet understood. 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, it has been demonstrated 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 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.

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