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Glial cell changes in epilepsy: Overview of the clinical problem and therapeutic opportunities

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ABSTRACT

It is estimated that one in 26 people will develop epilepsy in their lifetime, amounting to almost 12 million people in the United States alone (Hesdorffer et al., 2011). Epilepsy is a group of conditions characterized by sporadic occurrence of seizures and unconsciousness. This severely limits the ability to perform everyday tasks and leads to increased difficulty with learning and memory, maintenance of steady employment, driving, and overall socioeconomic integration. A greater understanding of the cellular and molecular mechanisms underlying seizures and epilepsy is necessary, as it may lead to novel antiepileptic treatments. In this chapter, we will review the current literature surrounding the involvement of glial cells in epilepsy with particular emphasis on review of human tissue studies and some possible underlying mechanisms. Based on the current evidence and hypotheses of glial mechanisms in epilepsy, novel therapeutic opportunities for the treatment of epilepsy will also be presented.

1. Introduction

It is estimated that one in 26 people will develop epilepsy in their lifetime, amounting to almost 12 million people in the United States alone (Hesdorffer et al., 2011). Epilepsy is a group of conditions characterized by sporadic occurrence of seizures and unconsciousness. This severely limits the ability to perform everyday tasks and leads to increased difficulty with learning and memory, maintenance of steady employment, driving, and overall socioeconomic integration. A greater understanding of the cellular and molecular mechanisms underlying seizures and epilepsy is necessary, as it may lead to novel antiepileptic treatments.

Most current antiepileptic drugs (AED) target neuronal voltage-gated sodium channels and calcium channels, glutamate receptors, or γ-aminobutyric acid (GABA) systems (Rogawski and Löscher, 2004). For example, Na^+ channel blockers such as phenytoin and carbamazepine reduce the frequency of neuronal action potentials, and GABA transaminase (GABAT) inhibitors, such as vigabatrin, increase GABA-mediated inhibition (Rogawski and Löscher, 2004). The mode of action of several commonly prescribed AEDs, such as valproate, is not entirely understood (Kwan et al., 2012; Perucca, 2005; Rogawski and Löscher, 2004). There are several drawbacks to the current AEDs. First, currently used AEDs often cause some form of cognitive impairment, including memory deficiencies and mental slowing (Aldenkamp et al., 2003). Cognitive impairments become particularly important in patients being treated with chronic AEDs. Moreover, polypharmacy has a more severe impact on cognitive function when compared to monotherapy, regardless of which type of AEDs are being used (Aldenkamp et al., 2003). Second, about 30% of patients being treated with AEDs, even with optimal current therapy, have poor seizure control and become medically refractory. In addition, adverse effects are frequently observed at drug doses within the recommended range (Perucca, 2005). Third, several studies have shown that there is an increased risk of teratogenicity in women with epilepsy who are receiving pharmacological treatment (Crawford, 2005; Wlodarczyk et al., 2012). For women taking enzyme-inducing AEDs, such as phenytoin or carbamazepine, hormonal forms of contraception are affected and the efficacy of oral contraceptive cannot be guaranteed (Crawford, 2005), thus complicating family planning.

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Finally, AEDs are associated with a number of adverse effects including mood alteration, suicidality, severe mucocutaneous reactions, hepatotoxic effects, decreased bone mineral density, weight management difficulties, skin rash, pseudolymphoma, and many others, which often leads to treatment failure (Perucca and Gilliam, 2012).

Even though it is recognized that there is a clinical unmet need for new AEDs, the market is crowded and not of high priority for the pharmaceutical industry (Bialer, 2012). Therefore, future designed new AEDs must have both the ability to prevent or delay the onset of epilepsy and have increased tolerability. Potential for treatment of non-epileptic CNS disorders is also preferred. It is noteworthy that anticonvulsants are one of the most commonly prescribed centrally active agents (Perucca, 2005) and are frequently used to treat other neurological disorders. One potential target that has been considered in recent years is glial cells.

2. Overview of glial function and changes in epilepsy

Over the last two decades, several lines of evidence have suggested that glial cells are potential therapeutic targets for the treatment of epilepsy and other central nervous system (CNS) diseases (Binder and Steinhäuser, 2006; Friedman et al., 2009). Glia are involved in many important physiological functions. For example, astrocytes play an established role in removal of glutamate at synapses, neuronal pathfinding, and the sequestration and redistribution of K^+ during neural activity (Ransom et al., 2003). Microglia are the resident CNS immune cells and are important for initiating the inflammatory response to brain injury and infection (Carson et al., 2006). Moreover, it is becoming increasingly clear that glial cells play a role in seizure susceptibility and the development of epilepsy (Binder et al., 2012; Binder and Steinhäuser, 2006; Clasadonte and Haydon, 2012; Friedman et al., 2009; Hsu et al., 2007; Seifert et al., 2010; Seifert et al., 2006; Tian et al., 2005). Direct stimulation of astrocytes leads to prolonged neuronal depolarization and epileptiform discharges (Tian et al., 2005). Glial cells can release neuroactive molecules and also modulate synaptic transmission through modifications in channels, gap junctions, receptors, and transporters (Beenhakker and Huguenard, 2010; Binder et al., 2012; Binder and Steinhäuser, 2006; Halassa et al., 2007; Hsu et al., 2007; Rouach et al., 2008; Santello et al., 2011; Tian et al., 2005; Volterra and Steinhäuser, 2004; Wang et al., 2012). Furthermore, striking changes in glial cell shape and function occur in various forms of epilepsy which may contribute to increased neuronal excitability and the development of epilepsy. Some of these changes include astroglial proliferation, dysregulation of water and ion channel expression, alterations in secretion of neuroactive molecules, and increased activation of inflammatory pathways (Binder et al., 2012; Clasadonte and Haydon, 2012; de Lanerolle and Lee, 2005; Heinemann et al., 2000; Hinterkeuser et al., 2000; Kivi et al., 2000; Seifert et al., 2006; Steinhäuser and Seifert, 2002). In addition to astroglial proliferation, recent evidence suggests that oligodendrocyte cell density is also increased in the white matter of the hippocampus and the neocortical temporal lobe in patients with temporal lobe epilepsy (Stefanits et al., 2012).

Evidence from studies in human tissue further suggests an important role for astrocytes in epilepsy. For example, astrocytes undergo activation to become reactive astrocytes in the epileptic brain (Clasadonte and Haydon, 2012; Heinemann et al., 2000). Changes in the expression of various astrocytic enzymes, such as adenosine kinase (Aronica et al., 2011) and glutamine synthetase (Coulter and Eid, 2012), contribute to the increased neuronal excitability found in epileptic tissue. In addition, microglia and inflammatory pathways contribute to the pathogenesis of seizures in various forms of epilepsy (Ravizza et al., 2008). In this chapter, we will review the current literature surrounding the involvement of glial cells in epilepsy with particular emphasis on review of human tissue studies and some possible underlying mechanisms. We will focus our attention on astrocytes and, to a lesser extent, microglia as there is more known about their role in epilepsy than other glial cell types. Based on the current evidence and hypotheses of glial mechanisms in epilepsy, novel therapeutic opportunities for the treatment of epilepsy will also be presented. For an overview of common seizure types and animal models of epilepsy, the reader is directed to Tables 1 and 2, respectively and to important reviews on these topics (Dvorak and Feit, 1977; Hodozuka et al., 2006; Raol and Brooks-Kayal, 2012; Roper et al., 1995).

3. Glial cell changes in temporal lobe epilepsy

Affecting over 40 million people worldwide (de Lanerolle et al., 2012), temporal lobe epilepsy (TLE) is characterized by recurrent seizure activity in the temporal lobe. TLE is the most common form of epilepsy found in adults and seizures are medically intractable in about 40% of patients suffering from this disease (Das et al.,

Table 1
Overview of seizure types.

Seizure type	Brief description	EEG characteristic
Focal	Seizure onset from one area of the brain and limited to one hemisphere	
Neocortical	Seizure generation from the neocortex; manifestation depends on exact location of origin and pattern of spread	
Temporal lobe	Seizure generation within the mesial structures, such as the hippocampus; often consists of epigastric aura followed by automatisms, dystonia of contralateral hand, and post-ictal confusion	
Multifactorial	Simultaneous seizure generation from two independent foci	
Generalized	Seizure onset simultaneously from both hemispheres	
Absence	Brief loss of consciousness, eye blinking and staring, and/or facial movements with no post-ictal confusion	3-Hz generalized spike-and-slow-wave complexes
Myoclonic	Quick, repetitive, arrhythmic muscle twitching involving one or both sides of the body; consciousness remains intact	Generalized spike-and-wave discharge
Clonic	Seizures consist of rhythmic muscle jerks during impaired consciousness	Fast activity (10 Hz) and slow waves with occasional spike-wave patterns
Tonic	An increase in muscle tone causes flexion of head, trunk, and/or extremities for several seconds	Bilateral synchronous medium to high-voltage fast activity (10–25 Hz)
Tonic–clonic	Tonic extension of muscles followed by clonic rhythmic movements and postictal confusion	Tonic phase: generalized rhythmic discharges decreasing in frequency and increasing in amplitudeClonic phase: slow waves
Atonic	Brief loss of postural tone, which can result in falls and injuries	Slow rhythmic (1–2 Hz) spike-and-wave complexes or more rapid, irregular multifocal spike-and-wave activity

Table 2
Common epilepsy types and models.

Epilepsy type	Brief description	Animal models
Temporal lobe	Spontaneous recurrent seizures arising from the temporal lobe; pathology often due to mesial temporal sclerosis	Electrical stimulation of limbic structures or hippocampal circuitry; kainic acid; pilocarpine; kindling (repeated low-intensity electrical stimulation)
Benign familial neonatal convulsions	Idiopathic neonatal epilepsy consisting of brief clonic movements lasting 2–3 min	Mutation in KCNQ2/3 gene
Febrile	Tonic–clonic seizures in infancy that occurs during fever; likely to have seizures later in life	Induced increase in core body temperature; mutations in SCN1A, SCN2A, or SCN1B subunit of sodium channel
Hypoxic-ischemic (HI)	Myoclonic jerks, automatisms, tonic–clonic head and limb movements due to lack of oxygen and/or restricted blood flow	Graded hypoxia with or without carotid ligation
West syndrome (infantile spasms)	Infantile epileptic spasms with sudden and brief flexion of body and extremities, hypsarrhythmia, poor developmental outcome	Mutations in ARX gene; corticotropin-releasing hormone (CRH) injection into the brain; intraperitoneal injection of NMDA; slow infusion of tetrodotoxin (TTX) into the neocortex or hippocampus; multiple hits of intracerebral injection of doxorubicin and lipopolysaccharide at p3 and p-chlorophenylalanine at p5
Focal cortical dysplasia	Malformation of cortical development that most commonly results in medically refractory epilepsy	Irradiation; focal contact freezing; kainic acid injection into lateral sites on the sensori-motor cortex
Post-traumatic	Traumatic brain injury (correlates with severity of injury)	Controlled cortical impact; fluid percussion; undercut; weight drop
Generalized seizures	Seizures that arise simultaneously from both hemispheres	Intraperitoneal injection of pentylenetetrazol; maximal electroshock seizures (MES); flurothyl

2012; de Lanerolle and Lee, 2005). Depth electrode studies have shown that most seizures originate from the hippocampus (de Lanerolle et al., 2003). The most common pathological feature found in these patients is hippocampal sclerosis, more generally known as mesial (Ammon's horn) temporal sclerosis (MTS), characterized by a pronounced loss of pyramidal neurons, granule cell dispersion, microvascular proliferation, synaptic reorganization, and reactive gliosis (Blümcke et al., 1999; Clasadonte and Haydon, 2012; de Lanerolle et al., 2012; Margerison, 1966). MTS was present in 30–58% of temporal lobe cases in both early and more recent autopsy studies (Binder and Steinhäuser, 2006; Bratz, 1899; de Lanerolle et al., 2003; Margerison, 1966; Sommer, 1880). When present, the sclerotic hippocampus is the predominant focus of seizure origin (Babb et al., 1984).

Previously, it was believed that neuronal loss led to astroglial phagocytosis and, consequently, increased gliosis (de Lanerolle and Lee, 2005). This view has changed, however, as reactive changes in astrocytes, or *reactive gliosis* (*astrogliosis*), is commonly found in both sclerotic and non-sclerotic hippocampal tissue specimens. These glial cell changes have become a hallmark of the sclerotic hippocampus and involve astrocyte hypertrophy (Binder and Steinhäuser, 2006; Borges et al., 2003; Briellmann et al., 2002; Das et al., 2012; Novozhilova and Gaikova, 2011; Shaprio et al., 2008; Van Paesschen et al., 1997), increased expression of glial fibrillary acidic protein (GFAP) (Das et al., 2012) and vimentin (Clasadonte and Haydon, 2012; Pekny and Nilsson, 2005; Wilhelmsson et al., 2004), and changes in glial specific proteins (Binder and Steinhäuser, 2006; Clasadonte and Haydon, 2012; Wilhelmsson et al., 2004). Astroglial changes that occur during the development of the disease will be reviewed in Chapter XX, while the effects of glial cells on synaptic strength will be discussed further in Chapter XX.

4. Changes in expression and distribution of glutamate receptors

Changes in expression, subunit composition, and functional properties of various astrocytic receptors have been examined in both experimental models and human tissue studies of epilepsy. Ionotropic glutamate receptors (GluRs) include *N*-methyl-D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtypes, each composed of common subunits that determine the physiological properties of the receptor. Human tissue studies of patients with MTS revealed expression changes of AMPA receptor subunits and an increase in receptor density that may contribute to enhanced excitability (de Lanerolle et al., 1998; Eid et al., 2002). Subunit expression of AMPA receptors in hippocampal glia differs from that of neurons. GluR2, which exhibits poor calcium permeability, is the most abundant in a subpopulation of glia now termed NG2 glia, and is often co-expressed with GluR4 (Seifert et al., 1997). Functional and molecular analysis of human hippocampus resected from patients with TLE revealed an increased expression of the glial GluR1 flip variant in the sclerotic hippocampus, suggesting that the increased flip/flop ratio may account for the prolonged receptor responses to increased glutamate release (Seifert et al., 2004; Seifert et al., 2002). If the GluR1 flip variant is co-expressed with GluR2, there is more incomplete receptor desensitization than the GluR2/GluR1 flop variant (Mosbacher et al., 1994).

Evidence is emerging that synaptic NMDARs may be most critical for normal brain function including synaptic plasticity and learning and memory, while extrasynaptic NMDARs may play a predominant role in pathological situations (Hardingham and Bading, 2010). It is especially noteworthy, then, that over the course of epileptogenesis there are significant changes in the distribution and subunit composition of NMDARs. The changes are complex, and involve an initial loss of synaptic NMDARs, likely due to neuronal loss, followed by increased NR2B subunit-subtype NMDARs located both extrasynaptically and ectopically expressed by astrocytes (Frasca et al., 2011). Elevated extrasynaptic expression of NMDARs by neurons would subject them to increased glutamate toxicity, while *de novo* expression of NR2B NMDARs by astrocytes would provide an additional astrocytic Ca^{2+} source that may contribute to release of gliotransmitters (discussed in further detail below). Ding et al. (2007) found that administration of the NR2B NMDAR antagonist ifenprodil after SE provided significant neuronal protection in a pilocarpine mouse model of epilepsy. Frasca et al. (2011) later obtained similar results using ifenprodil after SE in a stimulation model of spontaneous recurrent seizures. Therefore, pharmacological inhibitors of extrasynaptic NR2B NMDA receptors offer promise for reducing seizures and toxicity if used during the development of epilepsy, while also potentially leaving normal synaptic and cognitive function intact by sparing synaptic NMDARs. It will be important in future studies and possi-

ble human trials to monitor side-effects of pharmacological inhibitors of NR2B NMDARs, as the long-standing notion that NR2B subunits are only expressed by extrasynaptic NMDARs has been called into question in recent studies (Harris and Pettit, 2007; Rauner and Kohr, 2011).

There is also evidence for changes in expression levels of metabotropic glutamate receptors in reactive astrocytes. Made up of at least eight subtypes, mGluRs can be divided into three groups: Group I (mGluRs 1 and 5) is responsible for phosphoinositide hydrolysis; Group II (mGluRs 2-3) and Group III (mGluRs 4, 6-8) are negatively coupled to adenylyl cyclase. Several studies examining hippocampi from patients with TLE have found an increase in expression of mGluR2/3, mGluR4, mGluR5 (Notenboom et al., 2006; Tang et al., 2001) and mGluR8, suggesting that these receptors may play a role in gliosis. In accordance with these findings, an immunocytochemical study of human focal cortical dysplasia (FCD) specimens revealed that reactive astrocytes were intensely immunoreactive for mGluR2/3 and mGluR5 (Aronica et al., 2003). Changes in astrocyte mGluR expression may be very important in the development of epilepsy, as these receptors have been reported to play a role in gliovascular coupling (Gordon et al., 2008; Simard et al., 2003; Zonta et al., 2003), Ca^{2+}-dependent release of gliotransmitters (Angulo et al., 2004; Fellin et al., 2006c; Santello et al., 2011), and cell volume regulation (Gunnarson et al., 2008).

Alterations in ionotropic and metabotropic glutamate receptors have also been found in brain tumors associated with epilepsy (Rajneesh and Binder, 2009). For example, the expression of various glutamate receptor subtypes was examined in both gangliogliomas and dysembryoplastic neuroepithelial tumors from patients with intractable epilepsy. Immunolabeling revealed that mGluR2-3, mGluR5 and GluR5-7 were increased in reactive astrocytes in the perilesional zone when compared to the normal cortex (Aronica et al., 2001). Impaired glutamate uptake and neurotoxic release of glutamate from growing gliomas have been observed *in vitro* (Ye and Sontheimer, 1999). It is theorized that growing glial tumors actively kill surrounding neurons through the release of excessive quantities of glutamate, which may also contribute to the seizures frequently seen in conjunction with glioma (Buckingham et al., 2011; Ye and Sontheimer, 1999). This topic will be addressed in detail in Chapter XX.

5. Calcium-dependent release of gliotransmitters

Calcium-dependent gliotransmitter release from astrocytes has been hypothesized to directly contribute to excess neuronal synchronization that is seen in epileptic tissue (Carmignoto and Haydon, 2012; Navarrete et al., 2012). Although the extent to which this process takes place in healthy tissue is debatable (Fiacco et al., 2009; Fiacco et al., 2007), alterations in reactive astrocytes in epileptic tissue, including upregulation of mGluR expression, ectopic expression of NR2B subunit containing NMDARs, and secretion of proinflammatory mediators including TNFα, prostaglandins, and SDF-1α, play a powerful role in the ability of astrocyte Ca^{2+} elevations to release gliotransmitters including the excitatory transmitters glutamate and ATP (reviewed in Agulhon et al., 2012). Furthermore, it has been suggested that intracellular glutamate levels in astrocytes may be elevated due to increased glutamate uptake and decreased metabolic cycling (Eid et al., 2004), which may provide increased glutamate availability for packaging into synaptic-like microvesicles of astrocytes, which are thought to mediate Ca^{2+} dependent gliotransmission (Bergersen et al., 2011). Calcium-dependent glutamate release from astrocytes has been implicated in the initiation of epileptic seizure activity (Kang et al., 2005; Tian et al., 2005), although its necessity for seizure initiation has been questioned (Fellin et al., 2006a). A study using patch clamp recording and calcium imaging techniques in rat entorhinal cortex slices showed that an elevation in astrocytic Ca^{2+} correlated with the development and maintenance of a focal, seizure-like discharge (Gómez-Gonzalo et al., 2010). Spontaneous Ca^{2+} dependent oscillations were seen in astrocytes cultured from patients with Rasmussen's encephalitis, a rare form of intractable epilepsy (Manning and Sontheimer, 1997). It is speculated that spontaneous [Ca^{2+}] oscillations may promote hyperexcitability in epileptic tissue through astrocytic glutamate receptor activation (Manning and Sontheimer, 1997). Both ionotropic and metabotropic glutamate receptors expressed by reactive astrocytes are thought to contribute to the abnormal glutamatergic transmission commonly found in epileptic tissue. Furthermore, it was recently found in biopsied hippocampal tissue from epilepsy patients that agonist-evoked astrocyte Ca^{2+} elevations produced slow inward currents (SICs) in adjacent neurons (Navarrete et al., 2012). Earlier studies in acute tissue slices from rats found that SICs were associated with evoked and spontaneous astrocyte Ca^{2+} elevations (Angulo et al., 2004; Fellin et al., 2004; Parri et al., 2001). The exact relationship between SICs and epilepsy remains to be determined, but it is noteworthy that these events are large enough (up to several hundred pA) to drive neurons above firing threshold and are also locally synchronized among small groups of pyramidal neurons, raising the possibility that they represent small, initiating epileptic foci (Wetherington et al., 2008). SICs appear to be different from paroxysmal depolarization shifts (PDSs) or interictal discharges (Fellin et al., 2006), although this may depend on the specific epilepsy model used (Tian et al., 2005). Using the 4-AP model to evoke epileptiform activity in hippocampal slices, Tian et al. (2005) found that widespread astrocyte Ca^{2+} elevations preceded synchronized neuronal discharges, suggesting a causative role of astrocyte Ca^{2+} in seizure initiation *in vitro*. Furthermore, PDSs in this model persisted in TTX, making it difficult to dissociate SICs from PDSs. Further research will be necessary to understand the relationship between SICs and more traditional forms of epileptic activity. Interestingly, SICs can be evoked independently of astrocyte Ca^{2+} elevations, as will be discussed further below.

Another gliotransmitter that can be released by astrocyte Ca^{2+} elevations is ATP. ATP released from astrocytes exerts largely excitatory effects via the activation of the receptors P2X and P2Y (Boison et al., 2010). Dependent on both Ca^{2+} and SNARE proteins (Pascual et al., 2005), ATP release from astrocytes can modulate neuronal excitability (Domercq et al., 2006; Fellin et al., 2006b; Jourdain et al., 2007). ATP also acts as an extracellular messenger and a primary signal for calcium wave propagation (Carmignoto and Haydon, 2012; Clasadonte and Haydon, 2012). ATP release by astrocytes is likely to be enhanced in diseased or damaged tissue (Kuchibhotla et al., 2009), resulting in intercellular Ca^{2+} wave propagation across the astrocyte syncytium similar to what has been observed *in vitro* (Bowser and Khakh, 2007; Cornell-Bell et al., 1990). Enhanced astrocytic Ca^{2+} dynamics in epileptic tissue may promote neuronal excitability and synchronized discharges through a positive feedback loop of glutamate and ATP release. However, it is also important to consider that elevated ATP released by astrocytes will also elevate extracellular adenosine following rapid breakdown of ATP into adenosine (Zhang et al., 2003). Adenosine levels are also elevated during seizure activity (Dunwiddie, 1999; Winn et al., 1979). The powerful inhibitory effect of adenosine on excitatory synaptic transmission (see below) makes it difficult to determine whether increased release of ATP by astrocytes contributes to, or helps prevent, neuronal discharges and excitotoxicity.

6. Modulation of extracellular adenosine

Adenosine exerts a powerful inhibitory effect on excitatory synaptic transmission primarily through its interaction with presyn-

aptic A1 adenosine receptors (A1Rs) to suppress neurotransmitter release (Cunha, 2005; Dunwiddie and Diao, 1994; Haas and Selbach, 2000). Therefore, the cycle of adenosine release and breakdown is especially important in cases of excessive excitability including epilepsy. Once released from neurons and astrocytes, ATP is rapidly converted into adenosine monophosphate (AMP) and then into adenosine by extracellular nucleotidases (Dunwiddie et al., 1997). The reuptake of adenosine occurs through equilibrative nucleoside transporters (Dunwiddie and Diao, 2000), and phosphorylation by the astrocyte-specific enzyme adenosine kinase (ADK) breaks down adenosine and therefore clears excess adenosine from the extracellular space. Minor changes in ADK activity affect the active cycle between adenosine, AMP, ADK, and 5′-nucleotidase and lead to major changes in extracellular adenosine levels (Arch and Newsholme, 1978). Therefore, alterations in ADK are especially relevant to the generation of seizures. Increased levels of ADK are associated with seizures whereas decreased levels may lead to seizure suppression (Boison and Stewart, 2009). Increased ADK expression has been linked to seizure activity in both human tissue and experimental models of epilepsy (Aronica et al., 2011; Boison, 2012; Boison et al., 2010; Gouder et al., 2004). Seizure induction in experimental epilepsy was found to decrease extracellular adenosine concentrations through the upregulation of ADK (Boison, 2005). In the kainic acid model of TLE in mice, profound astrogliosis and increased ADK activity was observed (Gouder et al., 2004). This coincides with the findings of Aronica et al., who demonstrated prolonged increases in ADK – for at least 3–4 months – in the rat hippocampus and cortex after induction of status epilepticus. This increase was also detected in the hippocampus and temporal cortex of TLE patients (Aronica et al., 2011).

Collectively, the above findings led to the adenosine kinase hypothesis of epileptogenesis (Boison, 2012; Boison et al., 2010), including the dysregulation of ADK and its contribution to the epileptogenic cascade, which will be discussed in detail in Chapter XX. The therapeutic benefits of adenosine, adenosine receptor agonists, and ADK inhibitors has been widely recognized as effective seizure suppressors (Jacobson and Gao, 2006; Spedding and William, 1996; Williams, 1999; Williams and Jarvis, 2000). Intracranial injection of adenosine prevents seizures in rats (Anschel et al., 2004). In addition, the use of transgenic mice revealed that reduced forebrain ADK protects against epileptogenesis (Li et al., 2008). Other studies involving adenosine augmentation therapies (AAT) include a silk protein-based release system for adenosine (Wilz et al., 2008) and the local release of adenosine from grafted cells (Huber et al., 2001), both of which resulted in seizure suppression. Focal adenosine delivery, such as slow-release polymers, cellular implants, gene therapy, or pump systems, has been suggested as a new pharmacological tool to treat refractory epilepsy with minimal side effects (Boison and Stewart, 2009).

7. Astrocyte potassium and water channels

7.1. Potassium (K^+) channels

Astrocytes play a major role in K^+ homeostasis by moving K^+ away from areas of high concentrations to restore basal extracellular K^+ levels, a process called spatial buffering (Orkand, 1980). According to this model, the difference between glial syncytium membrane potential and local K^+ equilibrium potential at sites of high extracellular K^+ accumulation drives potassium ions into the astrocytic network. The inwardly-rectifying K^+ channel $K_{ir}4.1$ is the primary K^+ channel responsible for astrocyte K^+ uptake (Butt and Kalsi, 2006; Djukic et al., 2007). Once taken up into astrocytes, K^+ can then propagate through the glial network to sites of lower $[K^+]_o$ (Seifert et al., 2010). Mice deficient in astrocytic gap junction coupling exhibited impaired K^+ buffering, spontaneous epileptiform activity, and a decreased seizure threshold (Wallraff et al., 2006). The role of potassium and gap junction channels in tissue excitability will be discussed further in Chapter XX.

Human tissue studies have reported a significant loss of perivascular $K_{ir}4.1$ expression (~50%) in TLE patients, suggesting impaired spatial K^+ buffering in the epileptic hippocampus (Bordey and Sontheimer, 1998; Das et al., 2012; Heuser et al., 2012; Hinterkeuser et al., 2000; Kivi et al., 2000; Schröder et al, 2000). Rare human mutations in the human $K_{ir}4.1$ gene (KCNJ10) are associated with epilepsy (Haj-Yasein et al., 2011). Interestingly, two studies examined astrocytic K^+ currents in sclerotic and nonsclerotic hippocampi resected from epileptic patients. Using K^+-selective reference microelectrodes in area CA1 of human and rat hippocampal slices in combination with barium, a selective blocker of inwardly-rectifying K^+ channels in astrocytes, Heinemann et al. found K^+ elevation in non-sclerotic, but not in sclerotic, hippocampal tissue (Heinemann et al., 2000). A similar study found reduced astrocyte K^+ currents in hippocampal specimens from patients with MTS (Hinterkeuser et al., 2000). More recently, Heuser et al. found that the loss of astrocytic $K_{ir}4.1$ expression was most pronounced around vessels in gliotic areas of the sclerotic hippocampus of mesial temporal lobe epilepsy (MTLE) patients (Heuser et al., 2012). Thus, increasing evidence suggests that the dysregulation of K^+ spatial buffering may play a role in hyperexcitability, but how and when this occurs and its contribution to epileptogenesis remains unclear.

7.2. Water channels

Aquaporins (AQPs) are a family of small integral water transporting membrane proteins that exhibit a homotetrameric assembly in the lipid bilayer (Verkman, 2005). AQP4 is the predominant aquaporin in brain tissue as it is abundantly expressed in astrocytes and borders the subarachnoid space, ventricles, blood vessels, pia and osmosensory areas of the brain (Nielsen et al., 1997; Rash et al., 1998). It is tethered to the membrane via the adaptor syntrophin, a component of the dystrophin-associated protein complex (DAPC) (Amiry-Moghaddam et al., 2003a; Neely et al., 2001). Astrocytes mediate the redistribution of water, using AQP4 to facilitate glial water uptake at sites of neuronal activation and water efflux at distant sites (Nagelhus et al., 2004; Nielsen et al., 1997). The distribution of AQP4 in the hippocampus and its regulation and role in epileptogenesis have recently been investigated and extensively reviewed (Binder et al., 2012; Hsu et al., 2011; Lee et al., 2012).

Increased water content in the sclerotic human hippocampus was first suggested by an increased T2-weighted signal and decreased T1-weighted signal in magnetic resonance imaging (Mitchell et al., 1999); this was later confirmed with a higher diffusion coefficient in diffusion weighted imaging (Hugg et al., 1999; Lee et al., 2004). Lee et al. explored the molecular basis of the perturbed water homeostasis and found that AQP4 expression was increased in sclerotic, but not in non-sclerotic, hippocampi obtained from MTLE patients (Lee et al., 2004). Immunogold staining, however, revealed that AQP4 density along the perivascular membrane domain of astrocytes was decreased by 44% in the CA1 area of the hippocampus (Eid et al., 2005). Eid et al. also found decreased perivascular expression of dystrophin in sclerotic areas and postulated that a dysfunction in anchoring and localization of AQP4 to the membrane results in perturbed water flux and, consequently, impaired K^+ buffering capacity (Eid et al., 2005). Taken together, these results suggested that, although there is an overall increase in AQP4 expression, there was a redistribution of subcellular AQP4 in MTLE. This conclusion was supported by a recent study by Med-

ici et al. examining the cerebral cortex from patients with focal cortical dysplasia (FCD) type IIB, characterized by a distinctive malformation of cortical development, normal-appearing (cryptogenic) epileptic cortex, and nonepileptic control tissue (Medici et al., 2011). They found increased AQP4 expression with a polarized distribution in FCD type IIB tissue when compared to the nonepileptic or cryptogenic controls. Specifically, strong AQP4 immunoreactivity was found around dysplastic neurons whereas weak immunoreactivity was found around the vessels.

Might AQP4 upregulation be therapeutically feasible? So far there is no known pharmacological method to upregulate AQP4. However, several studies have examined indirect modulation of AQP4 expression. The neuronal isoform A4B8 of agrin, a heparan sulfate proteoglycan, increased protein levels of the M23 splice variant of AQP4 and increased swelling capacity of astrocytes when cultured in hypotonic medium (Noell et al., 2007). The glucocorticoid, triamcinolone acetonide (TA) was shown to induce AQP4 downregulation in the normal retina but increased expression in the inflamed retina (Zhao et al., 2011). Targeting the dystrophin-associated protein complex for increased expression has the potential to be a novel therapeutic target, but a way to modulate its expression in the brain is still unknown. Current studies focus on the role of dystrophin in Duchenne muscular dystrophy and a few have found ways to upregulate the anchoring protein (Kayali et al., 2012; Malerba et al., 2011), but the expression changes in brain tissue have not been examined.

8. Cell swelling and reduction of the extracellular space

It has been observed for some time from studies both *in vitro* and *in vivo* that hyperosmolarity protects against seizures, whereas hypoosmolarity promotes generalized seizures (Andrew et al., 1989; Dudek et al., 1990; Haglund and Hochman, 2005; Maa et al., 2011; Traynelis and Dingledine, 1989). The consequences of cell swelling and reduction of the extracellular space (ECS) include increased extracellular resistance (Andrew et al., 1989; Dudek et al., 1990), magnified effect of local extracellular ion and transmitter accumulation (Nagelhus et al., 2004; Schwartzkroin et al., 1998), and enhanced neuronal synchrony and excitability (Andrew et al., 1989; Traynelis and Dingledine, 1989).

A specific role for astrocyte swelling in increasing neuronal excitability is a compelling area for future investigation (Fig. 1). Astrocyte susceptibility to swelling during pathological states has been suspected for quite some time, dating back to early EM studies which noted that astrocytes "are very susceptible to edema and are among the first elements of the nervous system to swell in poorly fixed preparations" (Peters et al., 1991). Recent evidence based on real-time volume measurements using 2-photon microscopy indicates that astrocytes are much more prone to swelling than neurons (Andrew et al., 2007; Risher et al., 2009). Astrocyte susceptibility to volume changes has been attributed to selective expression of AQP4 (Amiry-Moghaddam et al., 2003b; Andrew et al., 2007; Nagelhus et al., 1999; Strohschein et al., 2011). During the buildup of excitability leading up to seizure (ictal) discharges, it is speculated that elevated K^+ released from neurons during synaptic transmission is taken up into astrocytes along with water, causing astrocyte swelling and progressive reduction of the ECS. There is strong evidence in cultured astrocytes *in vitro* that astrocyte swelling leads to opening of volume-regulated anion channels (VRAC) to produce a regulatory volume decrease. Release of water through astrocytic VRAC is accompanied by substantial amounts of glutamate (Abdullaev et al., 2006; Haskew-Layton et al., 2008; Kimelberg et al., 2006; Liu et al., 2006). Among the first targets encountered by astrocytically-released glutamate are extrasynaptic NMDARs, leading to SICs and potentially interictal and ictal (seizure-like) discharges. In support of this possibility, SIC-like currents have been evoked in CA1 pyramidal neurons by cell volume changes alone in acute hippocampal slices *in vitro* (Fiacco et al., 2007). Stimulation of NMDA receptors could be further enhanced by widespread Eph receptor – ephrin ligand interactions, facilitated by apposition of adjacent cellular membranes during reduction of the ECS. EphB2/ephrinB2 are known powerful potentiators of NMDA receptors (Grunwald et al., 2004; Henderson et al., 2001; Takasu et al., 2002), including NR2B NMDARs (Takasu et al., 2002), but their possible role in epilepsy has yet to be carefully examined.

The possibility for involvement of astrocyte swelling in seizure generation is even more compelling when taking into account the specific changes taking place in astrocytes during epileptogenesis. Loss and redistribution of AQP4 and $K_{ir}4.1$ away from astrocytic endfeet is expected to exacerbate astrocyte swelling by increasing water influx into astrocyte processes at synapses while decreasing efflux via endfeet into the cerebrovasculature (Wetherington et al., 2008). This could prolong seizures by slowing the recovery of astrocytic volume, a possibility supported by the increased seizure duration observed in AQP4 knockout mice (Binder et al., 2006). Upregulated expression of group I mGluRs in reactive astrocytes could further enhance modulation of AQP4 (Gunnarson et al., 2008) and exacerbate swelling and swelling-evoked release of glutamate by astrocytes. Increased release of ATP due to elevated secretion of inflammatory molecules and perhaps also by ectopic expression of NR2B NMDARs by astrocytes could significantly potentiate release of glutamate from VRACs as observed *in vitro* (Kimelberg, 2004; Mongin and Kimelberg, 2002). In addition, reduced expression of glutamine synthetase (Eid et al., 2004) would elevate cytoplasmic concentrations of glutamate in astrocytes, providing more glutamate to be released when VRACs open. Furthermore, Eph receptors and ephrins are upregulated following neural injury on different cell types, including reactive astrocytes, neurons and oligodendrocytes (Goldshmit et al., 2006). Extrasynaptic NR2B subunit NMDA receptor expression increases (Frasca et al., 2011), providing additional targets for astrocytically-released glutamate. All of these changes would be expected to exacerbate swelling, astrocytic release of glutamate, and stimulation of extrasynaptic NMDARs, contributing to the development of epilepsy and spontaneously recurring seizures. Although the therapeutic potential of inhibition of astrocytic VRAC has not yet been tested in epilepsy, the astrocyte-specific VRAC inhibitor DCPIB exhibits powerful neuroprotective effects in a rat model of ischemia (Zhang et al., 2008). Selective inhibition of astrocyte swelling, astrocyte glutamate release through VRAC, extrasynaptic NMDA receptors, and EphB2/ephrinB2 mediated NMDAR potentiation offer exciting avenues for the development of new strategies for the treatment of epilepsy.

A challenge facing future studies exploring specific astrocytic mechanisms of seizure generation and development of epilepsy is dissecting apart the relative contributions of astrocyte Ca^{2+} *vs.* astrocyte swelling. This is a particularly difficult endeavor given that astrocyte Ca^{2+} elevations resulting from receptor activation will occur alongside glutamate and potassium uptake, water influx, and cell volume changes. This issue is complicated further by a report suggesting that ATP-induced astrocyte Ca^{2+} elevations *in situ* activate VRAC (Takano et al., 2005). Furthermore, the changes taking place in reactive astrocytes during hippocampal sclerosis would be expected to affect both processes. However, tools are available to begin to differentiate between astrocyte Ca^{2+} sources and astrocyte swelling in the generation of epileptiform activity. Especially intriguing are the IP_3R2 knockout mice, in which astrocyte Ca^{2+} elevations are abolished (Petravicz et al., 2008). Neuronal SICs can be readily generated in hippocampal slices from IP_3R2 knockout mice (Fiacco et al., 2007) suggesting that SICs occur independent of astrocyte Ca^{2+} elevations. It will be especially interest-

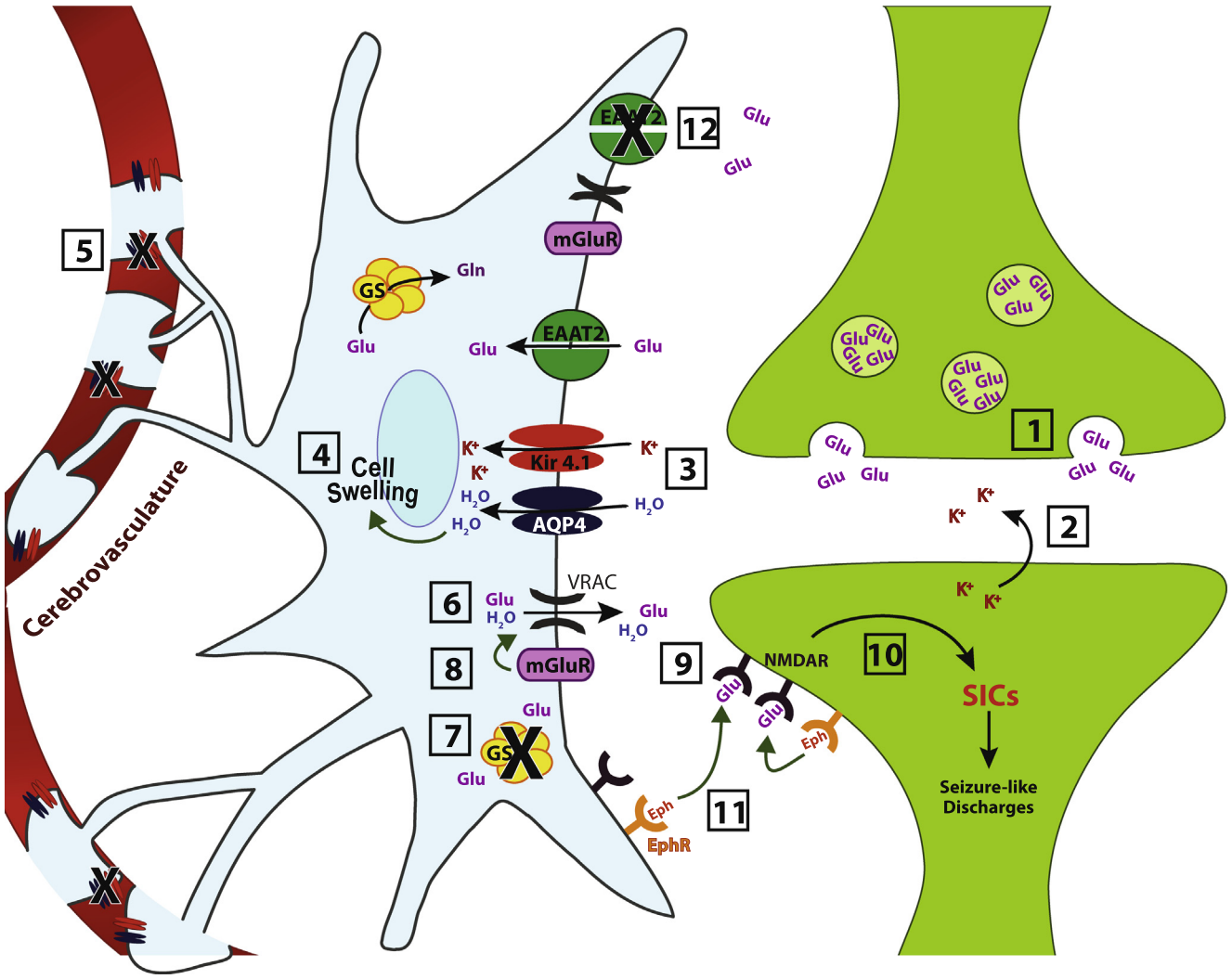

Fig. 1. Model for role of astrocyte swelling in neuronal excitability. At an excitatory synapse the neurotransmitter glutamate (Glu) is released from vesicles within the presynaptic terminal (1). Glu binds to receptors on the postsynaptic membrane and opens ion channels (not shown) allowing the movement of ions across the membrane, including the release of potassium ions (2). Elevated levels of K^+ are taken up by perisynaptic astrocytes along with water (H_2O) predominantly by $K_{ir}4.1$ potassium channels and aquaporin-4 (AQP4) channels, respectively (3). This leads to cell swelling and a reduction in extracellular space (4). Loss or redistribution of AQP4 and $K_{ir}4.1$ away from astrocytic endfeet (5) would exacerbate astrocyte swelling since water flux into astrocytes at synapses would be increased while efflux via endfeet into the cerebrovasculature would be decreased. Astrocyte swelling opens volume-regulated anion channels (VRACs), which release glutamate into the extracellular space (6). In addition, reduced expression of glutamine synthetase (GS) in the epileptic condition (7) elevates cytoplasmic concentration of glutamate in astrocytes, providing more glutamate to be released. Upregulation of metabotropic glutamate receptors (mGluRs) in reactive astrocytes could enhance AQP4-dependent swelling and swelling-evoked release of glutamate through VRACs (8). Astrocytically-released glutamate can then bind to extrasynaptic NMDA receptors (NMDARs) (9), generating slow inward currents (SICs) and potentially interictal and ictal (seizure-like) discharges (10). Facilitated by the close proximity of adjacent cellular membranes during cell swelling, Eph receptor (EphR) – ephrin (Eph) ligand interactions may further enhance the stimulation of NMDA receptors (11). EphRs, ephrins, and certain NMDA receptor subunits are upregulated after neural injury on different cell types, including reactive astrocytes and neurons. Reduced excitatory amino transporter 2 (EAAT2) expression in epileptic tissue may lead to delayed clearance of glutamate from the extrasynaptic space (12). All of the above mechanisms may contribute to astrocyte control of neuronal excitability.

ing in future studies using IP_3R2 KO mice to determine not only the extent to which astrocyte IP_3-mediated Ca^{2+} elevations play a role in the changes taking place during epileptogenesis, but also on the generation of epileptiform activity *in vitro* and *in vivo*. These mice might also be used to examine alternate Ca^{2+} sources in astrocytes that may become available over the course of epileptogenesis, such as astrocytic expression of NR2B NMDA receptors.

9. Glial glutamate transporters

Perturbations in glutamate homeostasis have been proposed to alter neuronal excitability and synchronization. Although glutamate transporters are expressed by several cell types, astrocytes are primarily responsible for the clearance of extracellular glutamate. This is due to the abundant expression of high-affinity glutamate transporter proteins called excitatory amino acid transporters (EAAT) on their cell surface (Danbolt, 2001). The transporter subtypes EAAT1 (GLAST) and EAAT2 (GLT1) are preferentially expressed by astrocytes (Coulter and Eid, 2012; Kim et al., 2011). The use of mice with deletion (Tanaka et al., 1997) or antisense oligonucleotide-mediated inhibition of synthesis (Rothstein et al., 1996) of EAAT2 (GLT1 in the rodent model) revealed that this transporter subtype is responsible for the bulk of glutamate uptake. Recent estimates suggest that EAAT2 is responsible for more than 90% of glutamate clearance in the brain, thus regulating the potentially toxic accumulation of glutamate in the extrasynaptic space (Kim et al., 2011). Once taken up by astrocytes, glutamate can potentially be released as a neurotransmitter or be metabolized into glutamine by the astrocyte-specific enzyme glutamine synthetase (GS) (Coulter and Eid, 2012).

Several clinical and experimental studies have suggested delayed clearance of extracellular glutamate in seizure development and spread (Campbell and Hablitz, 2004; Cavus et al., 2005; During and Spencer, 1993; Glass and Dragunow, 1995; Petroff et al., 2002; Tanaka et al., 1997). During and Spencer (1993) used intrahippocampal microdialysis to explore extracellular glutamate levels before and during seizure in human patients with complex partial epilepsy. They found higher levels of extracellular glutamate before a seizure and a sustained increase, to potentially neurotoxic levels, during a seizure (During and Spencer, 1993). Decreased EAAT2 protein expression has been found in the sclerotic hippocampus along with either increased (Mathern et al., 1999) or slightly decreased (Proper et al., 2002) expression of EAAT1. More recently, studies examining the dysplastic tissue of patients with focal cortical dysplasia (FCD) revealed a decrease in EAAT1 (Ulu et al., 2010), EAAT2 (González-Martínez et al., 2011; Ulu et al., 2010), and GS (González-Martínez et al., 2011). These findings support the hypothesis that reduced or dysfunctional glutamate transporters, particularly EAAT2, in the hippocampus may contribute to the pathogenesis of hippocampal sclerosis (During and Spencer, 1993). Other studies, however, found no change in expression of EAAT2 in tissue from patients with temporal lobe epilepsy (Eid et al., 2004; Tessler et al., 1999). Instead, a marked decrease in glutamine synthetase expression in the sclerotic hippocampus of TLE patients was observed (Eid et al., 2004; González-Martínez et al., 2011). These data support the hypothesis that impaired glutamate-glutamine cycling results in glutamate accumulation in the extracellular space (Cavus et al., 2005; Eid et al., 2004), and may also increase intracellular accumulation of glutamate in astrocytes which can then potentially be released through Ca^{2+} elevations or cell swelling. Regulation of astrocyte glutamine synthetase in epilepsy will be covered in greater detail in Chapter XX.

Modulation of glutamate uptake by astrocytes offers great potential for decreasing excessive excitability and hippocampal sclerosis associated with the development of epilepsy. Overexpression of GLT1 in transgenic mice attenuated epileptogenesis and reduced chronic seizure frequency in a pilocarpine-induced model (Kong et al., 2012). Until 2005, no pharmacological intervention was able to modulate GLT1 protein expression. Rothstein et al. showed that ceftriaxone, a β-lactam antibiotic, is a potent stimulator of GLT1 transcription and glutamate uptake (Rothstein et al., 2005), acting via the nuclear factor-κB signaling pathway (Lee et al., 2008), although these results are controversial (Carbone et al., 2012; Melzer et al., 2008). Ceftriaxone has been shown to reduce extracellular glutamate levels (Rasmussen et al., 2011) and have antiseizure effects (Jelenkovic et al., 2008; Zeng et al., 2010). The β-carboline alkaloid harmine can also increase GLT1 gene expression and glutamate uptake activity *in vitro* (Li et al., 2011). The β-lactamase inhibitors clavulanic acid and tazobactam decreased seizure-like activity in an invertebrate model (Rawls et al., 2010), although their effects on GLT1 have not been explored. Recently, however, the effectiveness of clavulanic acid as an antiepileptic therapeutic has been debated (Gasior et al., 2012; Huh et al., 2010). Nevertheless, the approach to upregulate GLT1 expression with these related β-lactam drugs remains to be explored fully in standard animal models of epileptogenesis.

10. Astrocyte glutamate transporters and glucose energy metabolism

Within the last few decades, it has become increasingly clear that astrocytes play a role in energy metabolism (Edmond et al., 1987; Hertz et al., 2007; McKenna, 2012; McKenna et al., 1993; Peng et al., 2001; Waagepetersen et al., 1998), and glutamate uptake via glial transporters is thought to be essential to brain metabolism (Alvestad et al., 2011; Hertz et al., 2007; Pellerin et al., 2002). One interesting hypothesis that has emerged over the years is known as the astrocyte-neuron lactate shuttle hypothesis (ANLSH). First introduced in 1994, Pellerin and Magistretti reported that glutamate stimulated glycolysis in astrocytes (Pellerin and Magistretti, 1994). According to this model, glutamate is released into the synaptic cleft at glutamatergic synapses. Excess extracellular glutamate is taken up by astrocytes via Na^+-dependent co-transport. Due to the increase of $[Na^+]_i$, the Na^+/K^+-ATPase gets activated and triggers glycolysis (use of glucose and production of lactate) within astrocytes. Lactate is then released via the plasma membrane lactate transporters MCT1 and MCT4 and is taken up by neurons where it enters the tricarboxylic acid (TCA) cycle and is used as an energy source to create adenosine triphosphate (ATP). Since then, while several studies have emphasized the ANLSH (Pellerin et al., 2007; Pellerin and Magistretti, 2012), this model is controversial because neurons also have glucose transporters (Mangia et al., 2009; Simpson et al., 2007) and recent evidence indicates the importance of oxidative phosphorylation as compared to glycolysis for neuronal energy production (Hall et al., 2012).

The metabolism of cerebral acetate takes place in glia. Over the years, exogenous acetate that has been labeled has become a common tool to study glial metabolism in the CNS (Badar-Goffer et al., 1990; Cerdan et al., 1990; Hassel et al., 1997; Hassel et al., 1992; Muir et al., 1986). Acetate is converted to acetyl-CoA and then oxidatively metabolized in the TCA cycle. In a recent study using the lithium–pilocarpine model of epilepsy, a significant increase in acetate uptake was observed throughout the brain in the acute phase of status epilepticus (SE) (Hosoi et al., 2010). In agreement with this, other studies using various models of TLE have demonstrated that although metabolic changes were primarily restricted to neurons within the epileptic circuit (Melo et al., 2005; Muller et al., 2000), a possible exception is a disturbed glutamate–glutamine cycle in astrocytes (Hammer et al., 2008; Melo et al., 2005; Muller et al., 2000). A possible role for glutamate metabolism in astrocytes in the etiology of absence epilepsy has also been suggested (Melo et al., 2007; Melo et al., 2006). Another study indicated that astrocytes may contribute to changes in glutamate and GABA metabolism, possibly due to a compromised branched-chain aminotransferase nitrogen shuttle and glutamine supply (Alvestad et al., 2008; Alvestad et al., 2011).

11. Neuroinflammation

Neuroinflammation is an integrated response of all CNS cell types, including microglia, macroglia, neurons, and infiltrating leukocytes to an initial injury. Innate immunity, or the early inflammatory response triggered by an insult, occurs in the brain after systemic infection. This phenomenon can eventually progress to an adaptive immune response in which the immune system can recognize and remember specific pathogens; this is mediated by activated lymphocytes recruited from the blood (Nguyen et al., 2002; Vezzani, 2012). When a local inflammatory reaction is triggered in the brain following an injury, both microglia and astrocytes become activated and release a number of proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). These proinflammatory mediators can alter the properties of both glial autocrine actions and glial-neuron paracrine signaling. Chronic progressive neurological disorders of the CNS, such as Alzheimer's disease, epilepsy, and stroke, are associated with changes in the antigen-presenting cell phenotype of microglia (Carson and Lo, 2007) as well as other glial responses. Further discussion of neuroinflammation and immunity in the brain will be provided in Chapter XX.

11.1. Gliosis and the inflammatory response in epilepsy

Specific inflammatory pathways are chronically activated during epileptogenesis in both microglia and astrocytes (Crespel et al., 2002; Ravizza et al., 2008). Along with astrogliosis, microglial activation has been shown within the sclerotic hippocampus of patients with TLE (Beach et al., 1995; Crespel et al., 2002; Ravizza et al., 2008; Sheng et al., 1994; Zattoni et al., 2011) and those exhibiting focal cortical dysplasia (FCD) (Boer et al., 2006; Iyer et al., 2010). Reactive astrocytes of lesioned areas in the hippocampus of MTLE patients overexpress NFkB-p65, a transcription factor that can activate the transcription of numerous proinflammatory genes (Crespel et al., 2002). Activated microglia and astrocytes chronically express IL-1β in the hippocampus of patients with TLE (Ravizza et al., 2008), which coincides with an increase in interleukin-1 receptor type I (IL-1RI) activation in the rat forebrain during status epilepticus (Ravizza and Vezzani, 2006). The infiltration of leukocytes into sclerotic tissue was detected in both human specimens and animal models using immunohistochemistry (Zattoni et al., 2011). Microglia activation and proliferation is prevalent in resected human epileptic tissue (Najjar et al., 2011).

Histological characteristics of FCD include cortical laminar disorganization and abnormal neuronal and astroglial cell types. Examination of the dysplastic cortex in FCD patients exhibiting seizures revealed increased microglial cells and macrophages, and increased number of CD-68- and HL-DR-positive cells (indicative of activated microglia) localized around blood vessels and dysplastic neurons (Boer et al., 2006; Iyer et al., 2010). Interestingly, the density of activated HLA-DR-positive microglial cells correlated with the duration of epilepsy and frequency of seizures (Boer et al., 2006). Ravizza et al. also found a positive correlation between the number of IL-1β and IL-1RI-positive neurons with seizure frequency and a negative correlation between IL-1ra-positive neurons and astroglial cells and the duration of epilepsy in FCD (Ravizza et al., 2006a).

Patients with tuberous sclerosis complex (TSC), an autosomal dominant disease that often presents with seizures, exhibit increased expression of members of the cytokine inflammatory pathway, including intracellular adhesion molecule-1 (CAM-1), TNFα, mitogen-activated protein kinase (MAPK), and NF-kB (Maldonado et al., 2003). In addition, increased microglial cells expressing class II antigens (HLA-DR) (Boer et al., 2008) and CD68-immunoreactive macrophages (Boer et al., 2008; Maldonado et al., 2003) suggesting activation of the proinflammatory signaling pathway, may contribute to cell death in TSC.

Both innate and adaptive immunity are activated in various forms of epilepsy. The complement pathway, an inflammatory response cascade that is part of innate and adaptive immunity, is overexpressed in reactive astrocytes, microglia, and macrophages in human TLE (Aronica et al., 2007; Aronica and Gorter, 2007), TSC (Boer et al., 2010; Boer et al., 2008), and FCD (Iyer et al., 2010). Alterations in blood brain barrier permeability were also associated with inflammation in TSC-associated lesions (Boer et al., 2010). A combination of proinflammatory cytokines and the components of the complement cascade may contribute to the spread of the inflammatory response and increased network excitability in the sclerotic hippocampus of patients with TLE, in lesions of patients with TSC, and in the dysplastic tissue of FCD.

11.2. Inflammation, encephalopathy, and epilepsy

The progressive inflammatory epileptic encephalopathy Rasmussen's encephalitis (RE) is characterized by uni-hemispheric lymphocytic infiltrates, microglial nodules, and neuronal cell loss (Bien et al., 2002). Stages of cortical pathology in RE vary from early inflammation, characterized by the infiltration of T lymphocytes and neuroglial reactions, to more severe stages of microglial reactivity (Wirenfeldt et al., 2009), extensive neuronal cell death, and cavitation of the cerebral cortex (Pardo et al., 2004). Moreover, these varying stages of inflammation can coexist in the same patient, which is consistent with an immune-mediated process. It is suspected that a T-cell mediated cytotoxic reaction, with lymphocytic infiltrates consisting of mainly $CD3^+$ and $CD8^+$ T cells (Wirenfeldt et al., 2009), induces neuronal death in RE (Bien et al., 2002; Pardo et al., 2004). The idea that an autoimmune process may underlie RE was conceived when the autoantibodies against glutamate-receptor subunit 3 (GluR3) were discovered (Rogers et al., 1994). Since then, GluR3 autoantigens have also been found in epilepsy patients with severe, early onset disease and intractable seizures, most often presenting in patients with frequent seizures (Mantegazza et al., 2002). Although the exact cause and underlying biochemical mechanism of RE is still unknown, there is strong evidence supporting the hypothesis of an antigen-driven major histocompatibility complex (MHC) class-I restricted, $CD8^+$ T-cell mediated attack against neurons and astrocytes in the CNS contributing to the pathogenesis in RE (Schwab et al., 2009).

11.3. Blood brain barrier and leukocyte infiltration

Seizure susceptibility has been linked to blood–brain barrier failure and the activation of peripheral white blood cells, although the molecular mechanisms of this cascade are still widely unknown. The migration of leukocytes, which are more abundant in human cortical CNS tissue of patients with epilepsy than in control tissue (Fabene et al., 2008), is controlled by chemokines in physiological and pathological conditions. Leukocyte–endothelium interactions and subsequent recruitment of leukocytes in brain parenchyma represent key components of the epileptogenic cascade (Fabene et al., 2010). In a mouse model of epilepsy, Fabene et al. (2008) found that seizures induced elevated expression of vascular cell adhesion molecules and enhanced leukocyte rolling and arrest in brain vessels mediated by the leukocyte mucin P-selectin glycoprotein ligand-1 (PSGL-1) and leukocyte integrins α4β1 and αLβ2. Moreover, the blockage of leukocyte-vascular adhesion attenuated blood brain barrier leakage, suggesting a pathogenic link between leukocyte-vascular interactions, BBB damage, and seizure generation (Fabene et al., 2008). Recent studies have demonstrated that lack of perforin, a downstream factor of natural killer (NK) and cytotoxic T cells, reduces BBB damage and mortality in the rat pilocarpine model of epilepsy (Marchi et al., 2011). This topic is covered in more detail in Chapter XX.

11.4. Anti-inflammatory modulation

Several studies have provided evidence in support of anti-inflammatory modulation for the treatment of epilepsy. A recent study used minocycline, a known inhibitor of inflammation, to determine whether innate immunity plays a causal role in mediating the long-term epileptogenic effects of early-life seizures (Abraham et al., 2012). Mice were induced with status epilepticus (SE) at postnatal day 25, which caused an increase in microglial activation. Mice induced with a second SE two weeks later responded with greater microgliosis and shorter latency to seizure expression. Minocycline abolished the acute seizure-induced microglial activation and decreased seizure susceptibility, suggesting that anti-inflammatory therapy after SE may be useful in blocking the epileptogenic process and mitigating the long-term damaging effects of early-life seizures. In a different study, treatment with aspirin, a non-selective cyclooxygenase inhibitor, reduced both the frequency and duration of spontaneous and recurrent seizures following pilocarpine-induced status epilepticus in rats (Ma et al., 2012). Moreover, aberrant migration of granule cells, mossy fiber sprout-

ing, and hippocampal neuronal cell loss were attenuated by aspirin.

The idea to block inflammation as a treatment for epilepsy is attractive but raises at least two problems. First, several immune agents and processes are triggered in response to an initial insult, and depression of all immune signaling would also depress the endogenous anti-inflammatory agents. Second, inflammation may contribute to the repair process that protects against major neuronal circuit changes that promote the emergence of spontaneous seizures (Dedeurwaerdere et al., 2012). A more sensible approach may be to target a single inflammatory cascade, such as regulation of the balance between brain IL-1β and IL-1ra (Vezzani et al., 1999; Vezzani et al., 2000). The exogenous application of IL-1β prolongs seizures in an IL-1R type I-mediated manner, and intrahippocampal application of recombinant IL-1ra inhibits motor and electroencephalographic seizures induced by bicuculline in mice (Vezzani et al., 2000). Inhibition of IL-1β production using selective inhibitors of interleukin-converting enzyme (ICE/caspase-1) or caspase-1 gene deletion have been shown to block seizure-induced production of IL-1β in the hippocampus of rats. Reduction in ICE/caspase-1 activity resulted in a significant decrease in seizure onset and duration (Ravizza et al., 2006b). A group of recent studies has indicated the importance of high-mobility group box-1 (HMGB1) release from neurons and glia and its interaction with Toll-like receptor 4 (TLR4), a key receptor of innate immunity (Maroso et al., 2010). It appears that the HMGB1-TLR4 axis is active in human epileptic tissue (Maroso et al., 2010; Zurolo et al., 2011), providing a new target for anti-inflammatory drug therapy (Aronica et al., 2012).

12. Conclusions and future directions

The underlying mechanisms and changes taking place in glial functioning during epilepsy remain poorly understood. While animal models and human tissue studies has provided some insight into glial involvement in epilepsy, both levels of investigation have certain limitations. Animal studies may not always accurately represent the disease progression as it is seen in humans; and on the other hand human tissue obtained from resected specimens does not allow determination of whether observed cellular and molecular changes are a cause or a consequence of epilepsy. Future studies should focus on identifying the morphological, biochemical, and electrophysiological glial cell alterations that occur prior to spontaneous seizure onset (*i.e.* during early epileptogenesis), as this could lead to a greater understanding of the disease. It may help to correlate the glial changes with newly developing imaging biomarkers of epilepsy, a topic discussed further in Chapter XX.

Current antiepileptic drugs focus on neuronal targets, mainly glutamatergic and GABAergic mechanisms or ion channels. These drugs often result in deleterious side effects including cognitive impairment. Moreover, a large subpopulation of patients does not respond to current AEDs, suggesting that there is a great need for new therapeutic directions. The evidence reviewed above indicates many functional changes in glial cells during epileptogenesis and in epileptic tissue. Changes in astrocyte transporters, receptors, and channels, and changes in inflammatory pathways have already revealed new potential therapeutic targets. Further dissection of the biochemical, morphological, and electrophysiological changes that occur in glial cells before, during, and after seizures and during the epileptogenic process will aid in the development of novel glial-specific antiepileptic therapies that will improve outcome.

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