Chapter 8
Crucial Role for Astrocytes in Epilepsy

Peter Bedner and Christian Steinhäuser

Abstract Epilepsy is characterized by the periodic occurrence of seizures. Currently available anticonvulsant drugs and therapies are insufficient to controlling seizures in about one third of patients. Thus, there is an urgent need for new therapies that prevent generation of the disorder and improve seizure control in individuals already afflicted. The vast majority of epileptic cases are of idiopathic origin with their underlying mechanisms being unclear. Neurosurgical specimens from patients presenting with mesial temporal lobe epilepsy (MTLE) demonstrate marked reactive gliosis. Since recent studies have implicated astrocytes in important physiological roles in the central nervous system, such as synchronization of neuronal firing, it is plausible they may also have a role in seizure generation and/or seizure spread. In support of this view, various membrane channels, receptors and transporters in astrocytic membranes are altered in the epileptic brain. Excitingly, recent evidence suggests that in the course of the pathogenesis of MTLE, these glial changes alter homeostatic network functions and temporally precede the alterations in neurons. These findings might eventually classify MTLE as a glial rather than a neuronal disorder, and identify astrocytes as promising new targets for the development of more specific antiepileptic therapeutic strategies.

This chapter summarizes current evidence of astrocyte dysfunction in epilepsy and discusses presumed underlying mechanisms. Although research on astrocytes in epilepsy is still in its infancy, the review clearly demonstrate a critical role of astrocytes in the disturbance of K^+ and transmitter homeostasis and its impact on seizure generation.

Keywords Epilepsy · Astrocyte · Gap junction · Connexin · Pannexin · K^+ clearance · Kir channel · Gliotransmitter release · Adenosine kinase · Glutamine synthetase · Inflammation · AQP4 channel

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8.1 Introduction

Astrocytes are active partners in neural information processing. Advanced electrophysiological and Ca^{2+} imaging techniques unraveled that these cells express a similar spectrum of ion channels and transmitter receptors as neurons, which allows them to sense and respond to neuronal activity. Despite the fact that the pathways enabling activation of astrocytes under physiological conditions are still ill-determined, evidence is emerging suggesting a critical role of astrocyte dysfunction in the pathogenesis of neurological disorders (Seifert et al. 2006). In this review we will discuss recent work on specimens from patients with pharmacoresistant mesial temporal lobe epilepsy (MTLE) and corresponding animal models of epilepsy, which revealed alterations in expression, subcellular localization and function of astroglial K^+ and water channels, resulting in impaired K^+ buffering. Dysfunction of glutamate transporters and the astrocytic enzymes, glutamine synthetase (GS) and adenosine kinase (ADK), as observed in epileptic tissue suggested that impaired astrocyte function is causative of hyperexcitation, seizure spread and neurotoxicity. Increasing evidence suggests that proinflammatory mediators cause dysfunctions in astrocytes, which individually or in concert provoke neuronal hyperexcitability. Accordingly, astrocytes should be considered as promising targets for new therapeutic strategies. We will summarize current knowledge of astrocyte dysfunction in MTLE and discuss putative mechanisms underlying these alterations.

8.2 Impaired K^+ Buffering in Epilepsy

8.2.1 K^+ Uptake and K^+ Spatial Buffering

Intense neuronal activity elicits transient increases in the extracellular potassium concentration ($[K^+]_o$) which under pathological conditions like epilepsy can reach values of up to 10–12 mM (Heinemann and Lux 1977). Even moderate rises in $[K^+]_o$ have been shown to significantly increase neuronal excitability and synaptic transmission (Balestrino and Somjen 1986; Walz 2000), underscoring the necessity of tight control of K^+ homeostasis for normal brain function. This task is mainly accomplished by astrocytes which are characterized by a very negative resting potential and a high resting permeability for K^+. Responsible for these glial membrane properties are essentially inwardly rectifying K^+ channels of the Kir4.1 subtype (Seifert et al., 2009). Astrocytes control $[K^+]_o$ by two mechanisms: K^+ uptake and spatial buffering (for review see Kofuji and Newman 2004). Net uptake of K^+ is mainly mediated by Na^+/K^+ pumps and $Na^+/K^+/Cl^-$ cotransporters and to a minor extent by Kir4.1 channels (D'Ambrosio et al. 2002; Kofuji and Newman 2004; Ransom et al. 2000). It is rather unlikely that this mechanism alone is sufficient for efficient clearance of excess $[K^+]_o$ since intracellular K^+ accumulation results in water influx and cell swelling. The spatial buffering model (Fig. 8.1) (Orkand

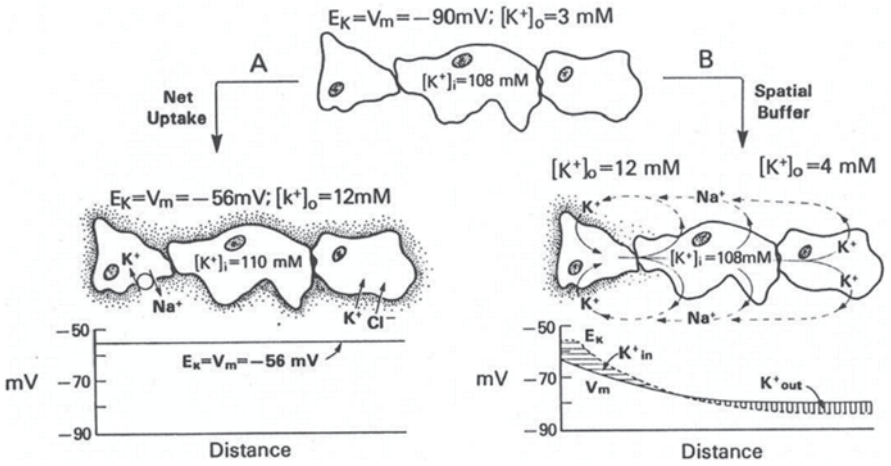

Fig. 8.1 Net uptake (*left*) and space-dependent spatial K^+ buffering (*right*). In case of spatial buffering (*right panel*), Activity in a group of neurons has produced local increase in $[K^+]_o$ to 12 mM (*shaded area, left*). This provokes a more positive membrane potential (V_m) that passively spreads through the coupled astrocytes. The positive shift of the K^+ equilibrium potential (E_K) is stronger than that of V_m of the cell exposed to high $[K^+]_o$ because the latter is "clamped" by the neighboring, more negative astrocytes exposed to lower (normal) $[K^+]_o$ (4 mM). The difference between E_K and V_m drives K^+ inward at the region where it is raised and outward at distant regions. The result is a net flux of K^+ away from the region where it has accumulated extracellularly. Average $[K^+]_i$ is not affected. The graph shows the distribution of E_K and V_m as a function of distance along the astroglial syncytium. (Modified from Orkand (1986), reproduced with permission)

et al. 1966) describes another, more effective mechanism for $[K^+]_o$ clearance. It is based on the fact that astrocytes are electrically connected to each other via gap junction (GJ) channels to form a functional syncytium. According to the model, excessive extracellular K^+ is taken up by astrocytes at sides of high neuronal activity redistributed through the astrocytic network to be released at regions of lower $[K^+]_o$. Here, uptake and release of K^+ occur passively, via passive diffusion through weakly-rectifying Kir4.1 channels. These channels are particularly well suited for this task because they possess a high open probability at resting potential and their conductance increases at high $[K^+]_o$ (Ransom and Sontheimer 1995). Intercellular K^+diffusion is also energy-independent, driven by the electrical gradient between the depolarized potential of glial cells at sides of K^+ entry and the more negative membrane potential of the glial syncytium (Orkand et al. 1966; Walz 2000; Kofuji and Newman 2004).

8.2.2 Kir4.1 Channels and K^+ Buffering in Epilepsy

Increased $[K^+]_o$ has been associated with the pathophysiology of epilepsy (Moody et al. 1974; Fisher et al. 1976; Lothman and Somjen 1976), and it is known that

high $[K^+]_o$ is sufficient to trigger epileptiform activity *in vitro* (Traynelis and Dingledine 1988). To assess the impact of Kir4.1 channels in K^+ buffering, the effect of Ba^{2+}-induced Kir channel block on stimulus-triggered rises in $[K^+]_o$ or iontophoretically applied K^+ was analyzed in sclerotic and non-sclerotic hippocampal slices from rat and man. It could be shown that Ba^{2+} significantly enhanced $[K^+]_o$ accumulation under control conditions, but had no effect in sclerotic hippocampi. These findings provided evidence for the disturbance of Ba^{2+}-sensitive K^+-uptake in sclerosis (Heinemann et al. 2000; Jauch et al. 2002; Kivi et al. 2000). Confirmation for this hypothesis came from patch clamp analysis, demonstrating significantly reduced Kir currents in the sclerotic CA1 region of neurosurgical specimens from patients presenting with MTLE (Hinterkeuser et al. 2000; Schröder et al. 2000; Bordey and Sontheimer 1998). Moreover, Western blot revealed a 50 % down-regulation of Kir4.1 protein in human hippocampal sclerosis (HS) compared to post-mortem controls (Das et al. 2012). In a recent study, Heuser et al. (2012) used immunohistochemistry to examine the distribution of Kir4.1 in hippocampi from MTLE patients. They found significantly reduced astrocytic Kir4.1 immunoreactivity in patients with HS compared to non-sclerotic and autopsy controls. Interestingly, the reduction was most pronounced around vessels and presumably caused by disruption of the dystrophin-associated protein complex in astrocytic endfeet (Heuser et al. 2012). Together, these studies imply that impaired K^+ clearance and increased seizure susceptibility in MTLE-HS result from reduced expression of Kir4.1 channels. However, it remains an open question whether this reduction represents cause, effect or adaptive response in TLE. In favor of a causative role for altered Kir channel expression in epilepsy, David et al. (2009) showed in an albumin model of epilepsy that Kir4.1 down-regulation occurs before the onset of epileptic activity. Another study, however, reported no changes in astrocytic Kir currents 7–16 days following systemic injection of kainate, implying that Kir down-regulation represents a consequential event in epilepsy (Takahashi et al. 2010).

Further support for the crucial role of Kir4.1 in glial K^+ buffering emerged from the phenotype of Kir4.1 knockout mice (Djukic et al. 2007; Kofuji et al. 2000). Global deletion of the Kir4.1 encoding gene, *KCNJ10*, resulted in marked motor impairments and premature death (postnatal day 8 (P8) to P24) (Neusch et al. 2001). Mice with glia-specific deletion of Kir4.1 (cKir4.1$^{-/-}$ mice) displayed a similarly severe phenotype, including ataxia, seizures and early lethality before P30. At the cellular level, these mice showed substantial depolarization of gray matter astrocytes and consequently severely impaired astrocytic K^+ and glutamate uptake (Djukic et al. 2007). Similar results were obtained after down-regulation of Kir4.1 by RNAi in cultured astrocytes (Kucheryavykh et al. 2007). Follow-up studies performed on cKir4.1$^{-/-}$ animals substantiated the crucial role of Kir4.1 channels in K^+ buffering and demonstrated that loss of Kir4.1 expression causes epilepsy (Chever et al. 2010; Haj-Yasein et al. 2011).

Missense variations in the *KCNJ10* gene have been linked to seizure susceptibility in man (Buono et al. 2004). Loss-of-function mutations in *KCNJ10* underlie an

autosomal recessive disorder characterized by seizures, ataxia, sensorineural deafness, mental retardation and tubulopathy (EAST/SeSAME syndrome) (Bockenhauer et al. 2009; Scholl et al. 2009; Reichold et al. 2010; Williams et al. 2010). Patients suffering from this disorder display focal and generalized tonic-clonic seizures since childhood. Another study reported that autism with seizures and intellectual disability is tentatively linked to gain-of-function mutations in *KCNJ10* (Sicca et al. 2011). Heuser et al. showed that a combination of three single nucleotide polymorphisms (SNPs) in the aquaporin 4 (AQP4) gene (encoding a water channel) together with two SNPs in the *KCNJ10* gene was associated with MTLE (Heuser et al. 2010). Association analysis in MTLE patients with a history of febrile seizures (FS) versus such without FS revealed that a combination of SNPs in *KCNJ10, AQP4*, and the area between *KCNJ10* and *KCNJ9* was significantly associated with MTLE-FS (Heuser et al. 2010).

8.3 GJ Communication in Epilepsy

8.3.1 Potential Roles of GJs in Epilepsy

Astrocytes in the adult brain are connected to each other via GJ channels composed of connexin43 (Cx43) and Cx30 (Nagy and Rash 2000), allowing intercellular exchange of ions, second messengers, nutritional metabolites and amino acids. The astroglial syncytium has important functions, including spatial buffering of K^+ ions (see above), trafficking and delivery of energetic metabolites to neurons (Giaume et al. 1997), intercellular propagation of Ca^{2+} waves (Scemes and Giaume 2006), volume regulation (Scemes and Spray 1998), and adult neurogenesis (Kunze et al. 2009; reviewed by Pannasch and Rouach 2013).

The role of interastrocytic gap junctional coupling in the development and progression of epilepsy is still controversial (for review see Nemani and Binder 2005; Carlen 2012; Steinhäuser et al. 2012). According to the spatial buffering concept (see above) the astroglial network is expected to possess antiepileptic function, since reduction of astrocytic coupling would result in accumulation of extracellular K^+ and, consequently, to neuronal depolarization and a lowered threshold for seizure generation. In line with this hypothesis are results from transgenic mice with coupling-deficient astrocytes ($Cx30^{-/-}$ $Cx43^{flox/flox}$ hGFAP-Cre mice; dko mice). In these mice, clearance of K^+ but also glutamate was disturbed. Consistently, these mice displayed spontaneous epileptiform events, a reduced threshold for the generating epileptic activity (Fig. 8.2), increased synaptic transmission and enhanced activity-induced astrocytic swelling (Wallraff et al. 2006; Pannasch et al. 2011). Although these findings strongly support an anticonvulsive role of glial GJ networks, a potential seizure-promoting role emerged from the results by Rouach et al. (2008). They elegantly demonstrated that astroglial GJs mediate activity-dependent intercellular trafficking of metabolites from blood vessels to sites of high energy

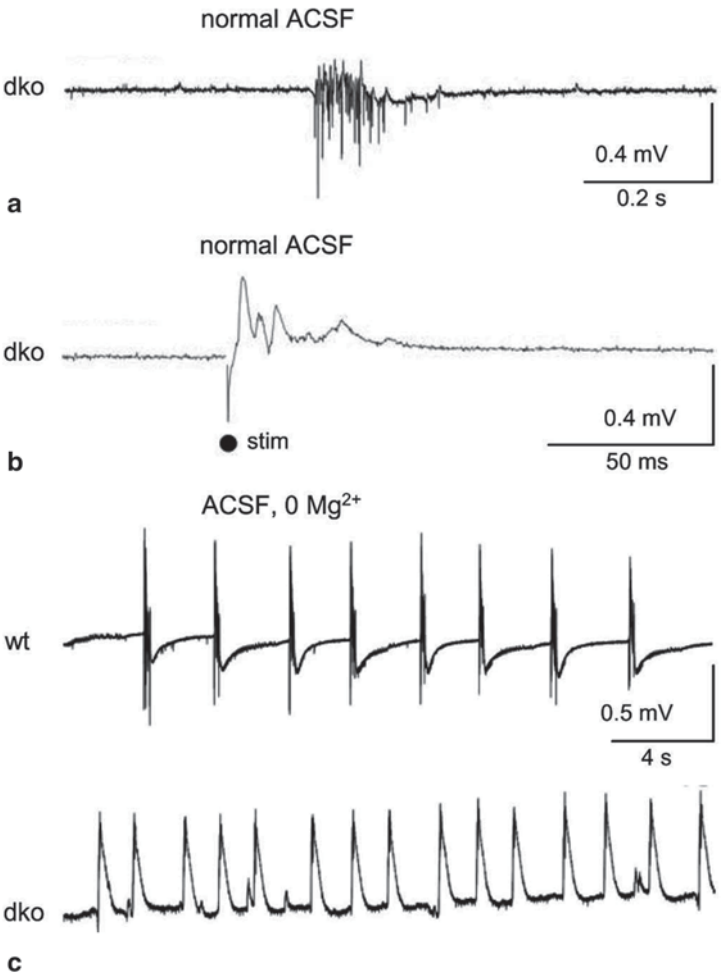

Fig. 8.2 Epileptiform field potentials (EFPs) in CA1 region of dko mice. **a** Spontaneous EFPs (CA1 region) occurred only in slices, bathed in artificial cerebrospinal fluid (*ACSF*), from dko mice but not in wild type (*wt*) mice (not shown). **b** Similarly, low-intensity Schaffer-collateral stimulation gave rise to EFPs only in dko slices. **c** EFPs induced by washout of Mg^{2+} (0 Mg^{2+}) were more frequent in dko slices and occurred with shorter latency. Original traces from wt (*top*) and dko (*bottom*) mice. (From Wallraff et al. (2006), reproduced with permission)

demand, suggesting that this process is essential for the maintenance of synaptic activity under pathological conditions such as epilepsy. Additionally, involvement of GJ channels in the intercellular spread of Ca^{2+} waves favors a proconvulsive role of the astroglial syncytium, since alterations in the astrocytic coupling would influence the propagation of Ca^{2+} waves and, therefore, neuronal synchronization and spread of ictal activity (Gomez-Gonzalo et al. 2010). Taken together, astroglial GJ networks might play a dual role in epilepsy, combining pro- and antiepileptic

properties. Further work is needed to elucidate which of the mechanisms prevails under various circumstances.

8.3.2 Connexin Expression and Coupling in Epileptic Tissue

Seizure-induced changes in Cx expression have been investigated in several studies using a variety of animal models and human tissue (for reviews see Nemani and Binder 2005; Giaume et al. 2010; Steinhäuser et al. 2012). The results are conflicting and do not allow drawing definitive conclusions. In animals, increased (Gajda et al. 2003; Samoilova et al. 2003; Szente et al. 2002; Condorelli et al. 2002; Takahashi et al. 2010; Mylvaganam et al. 2010), unchanged (Khurgel and Ivy 1996; Li et al. 2001; Söhl et al. 2000; Xu et al. 2009) and decreased (Elisevich et al. 1997a, 1998; Xu et al. 2009; David et al. 2009) Cx43 and/or Cx30 transcript and/or protein have been reported. This inconsistency might be explained by differences between animal models, seizure duration and investigated brain area. In human specimens, mainly up-regulation of Cx43 transcript and/or protein has been described (Aronica et al. 2001; Collignon et al. 2006; Fonseca et al. 2002; Naus et al. 1991), although unchanged levels have also been reported in one study (Elisevich et al. 1997b). However, Cx expression does not necessarily reflect the extent of functional coupling, since post-translational modifications, such as phosphorylation, might alter GJ channel unitary conductance, open probability, trafficking or internalization. Hence, functional coupling analyses are indispensable to receive reliable results. Increased astrocytic coupling has been reported in a post-*status epilepticus* (SE) rat model of epilepsy (Takahashi et al. 2010), and in hippocampal slice cultures chronically exposed to bicuculline (Samoilova et al. 2003). In contrast, Xu et al. observed significantly reduced coupling in the hippocampal CA1 region in a genetic mouse model of tuberous sclerosis complex (Xu et al. 2009). Human coupling studies have so far only been performed on primary astrocyte cultures derived from epileptic specimens (Lee et al. 1995). Using fluorescence recovery after photobleaching (FRAP), these authors found enhanced astrocyte coupling in cells from epileptic specimens.

Another approach to assess the role of GJ channels in epilepsy is pharmacological disruption of inter-astrocytic communication through GJ blockers, substances producing intracellular acidification or Cx mimetic peptides. Such experiments have been performed in a variety of *in vivo* and *in vitro* animal models of epilepsy (Bostanci and Bagirici 2006, 2007; Gajda et al. 2003; Gigout et al. 2006; Jahromi et al. 2002; Kohling et al. 2001; Medina-Ceja et al. 2008; Perez-Velazquez et al. 1994; Ross et al. 2000; Samoilova et al. 2003, 2008; Szente et al. 2002; Voss et al. 2009). Most of these studies reported anticonvulsive effects of GJ inhibition although opposite effects were observed in the study by Voss et al. (2009). In neocortical slices from patients with MTLE or focal cortical dysplasia, GJ blockers attenuated spontaneous and evoked epileptiform activity (Gigout et al. 2006). Major problems with using GJ blockers are their significant side effects and poor Cx isoform-specificity.

In conclusion, Cx expression studies, functional coupling analyses and uncoupling experiments yield an inconsistent picture on the role of the astroglial network in the pathophysiology of epilepsy. Further work is needed to clarify this issue.

8.3.3 Role of Cx Hemichannels and Pannexin Channels in Epilepsy

In addition to inter-cellular communication, functional membrane-spanning Cx hemichannels (HCs) have been demonstrated in astrocytes. These channels are non-selective and permeable for large molecules, such as ATP, glutamate, glucose and glutathione. Under normal conditions these channels are closed, but the open probability increases upon depolarization, altered intra- and extracellular Ca^{2+} concentration, metabolic inhibition or proinflammatory cytokines (reviewed by Theis and Giaume 2012; Orellana et al. 2009, 2013). It has been suggested that activated HCs promote neuronal hyperactivity and synchronization through excessive release of ATP and glutamate, which in turn increases excitability and Ca^{2+} wave propagation (Bedner and Steinhäuser 2013). GJ channels and HCs are oppositely regulated by proinflammatory cytokines (Meme et al. 2006; Retamal et al. 2007) and may play differential roles in epilepsy. Indeed, Yoon et al. (2010) showed in hippocampal slice cultures exposed to bicuculline that selective inhibition of HCs by low concentrations of mimetic peptides had protective effects on seizure spread while blockade of both HCs and GJs by high doses of the peptide exacerbated the lesion.

In addition to the Cx HCs, another family of proteins, termed pannexins (Panx1–3), can form functional transmembrane channels (but not inter-cellular channels) in different cell types, including astrocytes and neurons. Like Cx HCs, pannexins possess a very low open probability at rest, which increases upon elevated $[K^+]_o$, depolarization, increased intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), mechanical stress and $P2X_7$ receptor activation (Scemes and Spray 2012; Suadicani et al. 2012). It has been hypothesized that Panxs contribute to seizures by releasing ATP (Santiago et al. 2011). Indeed, increased Panx transcript levels have been found in an *in vitro* seizure model (Mylvaganam et al. 2010). Moreover, pharmacological inhibition or genetic deletion of Panx1 resulted in reduced seizure activity during kainate-induced SE (Santiago et al. 2011).

8.4 Aquaporin-4 Dysfunction and Epilepsy

8.4.1 Role of Aquaporin-4 in Epilepsy

The aquaporins (AQPs) are a family of small (24–30 kDa) integral proteins that mediate transmembrane water movement in response to osmotic gradients. So far, fourteen AQPs have been identified in mammals. AQP4 is the predominant water

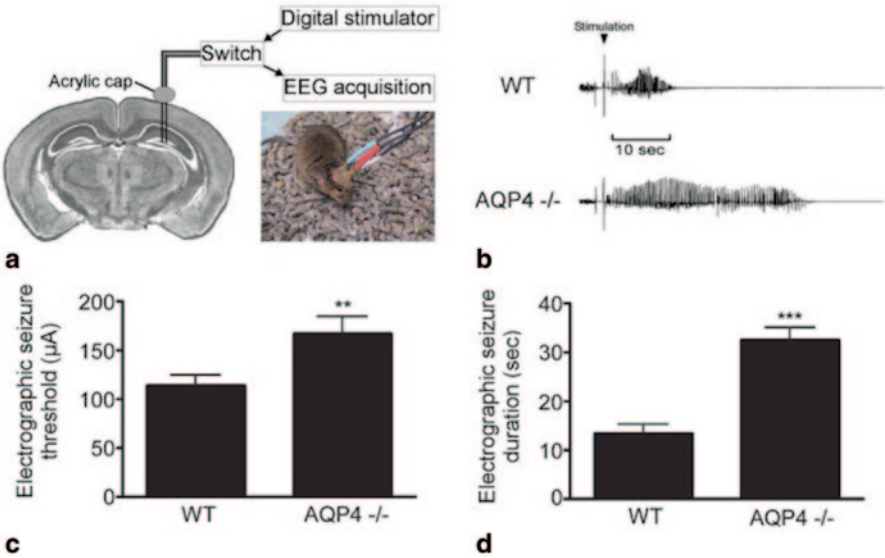

Fig. 8.3 Electrographic seizure threshold and duration in wt vs. AQP4$^{-/-}$ mice. **a** Bipolar electrodes implanted in the right hippocampus, and sealed to the skull by an acrylic cap, were connected to a stimulator and an EEG acquisition system. Mice were awake and behaved normally at the onset of stimulation (*inset*). **b** EEG from wt and *Aqp4*$^{-/-}$ mice. Baseline EEG prior to stimulation is similar (*left*). Hippocampal stimulation-induced electrographic seizures are shown for a wt (*top*) and an *Aqp4*$^{-/-}$ mouse (*bottom*). Note the prolonged seizure of the *Aqp4*$^{-/-}$ mouse. Behavioral arrest was observed in both animals during the seizure. Postictal depression is evident on the EEG in both mice. **c** *Aqp4*$^{-/-}$ mice had a higher electrographic seizure threshold than wt controls. **d** *Aqp4*$^{-/-}$ mice had remarkably longer stimulation-evoked seizures compared to wt controls. (From Binder et al. (2006), reproduced with permission)

channel in the brain, where it is mainly localized to astrocyte perivascular endfeet as well as perisynaptic processes (for review see Binder et al. 2012; Papadopoulos and Verkman 2013). AQP4 has been implicated in the pathogenesis of epilepsy mainly due to their role in regulating extracellular fluid osmolarity and extracellular space (ECS) volume (Schwartzkroin et al. 1998). Indeed, several studies have demonstrated that osmolarity-induced reduction in the ECS volume causes neuronal hyperexcitability (Dudek et al. 1990; Roper et al. 1992; Chebabo et al. 1995; Pan and Stringer 1996), while increasing the ECS volume attenuates epileptiform activity (Traynelis and Dingledine 1989; Dudek et al. 1990; Pan and Stringer 1996; Haglund and Hochman 2005). In addition to ECS volume regulation, the spatial overlap of AQP4 with Kir4.1 in glial endfeet gave rise to the hypothesis that AQP4 may be involved in K^+ homeostasis (Binder et al. 2012).

Mechanistic insight into the role of AQP4 in ECS volume regulation, K^+ clearance and neuronal excitability came from transgenic mice. AQP4-deficient (AQP4$^{-/-}$) mice display mild ECS volume expansion as assessed by FRAP and the tetramethylammonium method (Binder et al. 2004b; Yao et al. 2008). In acute seizure models, AQP4$^{-/-}$ mice exhibited elevated seizure threshold but prolonged seizure duration (Fig. 8.3) and enhanced frequency of spontaneous seizure during

the early phase (Binder et al. 2004a; Binder and Steinhäuser 2006; Lee et al. 2012). In addition, *in vivo* and *in situ* studies using K^+ sensitive electrodes or a fluorescent K^+ sensor revealed impaired stimulus-induced $[K^+]_o$ clearance in AQP4-deficient mice (Binder and Steinhäuser 2006; Padmawar et al. 2005; Strohschein et al. 2011). Interestingly, K^+ spatial buffering was enhanced in AQP4$^{-/-}$ mice, probably due to improved GJ coupling (Strohschein et al. 2011). The expanded ECS volume found in AQP4-deficient mice offers an explanation for the elevated seizure threshold of these mice, while the impaired K^+ uptake might account for the prolonged duration and increased frequency of seizures. As described in Sect. 8.2.1 above, insufficient $[K^+]_o$ clearance would result in neuronal hyperexcitability. However, the mechanistic link between AQP4 expression and K^+ homeostasis has not been resolved so far. The view of a functional interaction between the AQP4 and Kir4.1 (Nagelhus et al. 1999) is not supported by follow-up studies showing AQP4-independent Kir4.1 function (Ruiz-Ederra et al. 2007; Zhang and Verkman 2008; Strohschein et al. 2011). A more reasonable hypothesis implies that astrocytic K^+ uptake during neuronal activity triggers AQP4-dependent osmotic water uptake and, therefore, reduction of the ECS. ECS shrinkage, in turn, causes an increase of $[K^+]_o$ and consequently further K^+ uptake by astrocytes (Papadopoulos and Verkman 2013). Recently, this hypothesis was supported by mathematical modeling (Jin et al. 2013).

8.4.2 AQP4 Expression and Regulation in Epileptic Tissue

AQP4 expression was investigated in hippocampi from MTLE patients using rtPCR, immunohistochemistry and gene chip analysis (Lee et al. 2004). The authors found enhanced AQP4 levels in HS, but reduced expression of the dystrophin gene, which encodes the protein that is involved in anchoring AQP4 in perivascular endfeet, and speculated that polarity in astrocytic AQP4 distribution got lost. This finding was subsequently confirmed with immunogold electron microscopy and Western blot analysis (Eid et al. 2005). This locally restricted reduction of AQP4 was accompanied by a loss of perivascular dystrophin, indicating that AQP4 mislocalization was caused by a disrupted dystrophin complex. Similar loss of perivascular AQP4 and dystrophin were found in tissue from patients with focal cortical dysplasia (Medici et al. 2011). Further indication for the involvement of AQP4 in epilepsy and for the proposed interplay between AQP4 and Kir4.1 comes from genetic studies showing that several SNPs in the *KCNJ10* and *AQP4* genes are associated with MTLE (Heuser et al. 2010; see also paragraph 2.2).

In a recent study, Alvestad et al. (2013) explored, in the kainate model, whether the loss of perivascular AQP4 found in human MTLE is involved in epileptogenesis or merely represents a consequence of the condition. They could demonstrate that AQP4 mislocalization precedes the chronic phase of epilepsy, suggesting that astrocytic dysfunction is of pathophysiological relevance.

8.5 Altered Glutamate Homeostasis in Epilepsy

8.5.1 Extracellular Glutamate Levels in MTLE

Astrocytes modulate synaptic transmission and neuronal excitability by controlling extracellular neurotransmitter concentrations in the central nervous system (CNS). Rapid clearance of excessive glutamate from the ECS as well as its recycling is essential for survival and normal brain function. To prevent excitotoxic accumulation of glutamate in the ECS, glutamate is taken up by astrocytes via specialized transporters, converted to glutamine by GS and shuttled back to neurons for re-synthesis of glutamate. Dysfunction of the glutamate metabolism has been proposed to be critically involved in the pathophysiology of epilepsy (Eid et al. 2008b; Coulter and Eid 2012). This assumption is supported by the fact that glutamate and glutamate analogs cause seizures and neuronal loss in experimental epilepsy (Olney et al. 1972; Nadler and Cuthbertson 1980; Ben-Ari 1985; Fremeau et al. 2002). Moreover, increased interictal glutamate levels and stronger seizure-induced glutamate transients were found in the hippocampi of MTLE patients (Cavus et al. 2005; During and Spencer 1993). Among MTLE patients, those with HS displayed higher interictal extracellular glutamate levels (Petroff et al. 2003; Coulter and Eid 2012). However, as discussed by Coulter and Eid (2012), the source of glutamate in HS is obscure, since one of the hallmarks of this pathology is loss of glutamatergic neurons in the hippocampal CA1 region.

8.5.2 Astrocytic Glutamate Uptake in Epilepsy

Astrocytes take up glutamate from the ECS via high-affinity glutamate transporters (excitatory amino acid transporters, EAATs), which utilize the electrochemical gradient of Na^+ and K^+ as a driving force. Five transporter isoforms have been identified and two of them, GLAST (in rodents; in human EAAT1) and GLT1 (in rodents; in human EAAT2), are preferentially expressed in astrocytes. The impact of astrocytic glutamate uptake became obvious from the phenotype of genetically engineered mice devoid of transporter proteins. GLT1 knockout mice displayed lethal spontaneous seizures, increased susceptibility to acute cortical injury and seizures after administration of subconvulsive doses of pentylenetetrazole (PTZ) (Tanaka et al. 1997). Consistently, pharmacological inhibition of GLT1 in rat neocortex reduced the threshold for evoking epileptiform activity (Demarque et al. 2004; Campbell and Hablitz 2004). In contrast, antisense knockdown of GLT1 in adult rats caused increased extracellular glutamate, but not seizures (Rothstein et al. 1996). Mice deficient in GLAST showed no spontaneous seizures or electroencephalography (EEG) paroxysmal discharges, but amygdala kindling or PTZ-induced seizures were of longer duration, more severe and occurred after a shorter latency in mutant mice (Watanabe et al. 1999).

In MTLE patients, inconsistent data on the regulation of EAAT1 and 2 have been published; no changes in transporter expression (Tessler et al. 1999; Eid et al. 2004) or decreased levels of EAAT 1/2 were found in epileptic hippocampi (Mathern et al. 1999; Proper et al. 2002). In kindled rats, unchanged GLT1 and GLAST levels were described (Akbar et al. 1997; Miller et al. 1997; Simantov et al. 1999) while decreased levels were found in the pilocarpine (Lopes et al. 2013) and albumin models (David et al. 2009) as well as in a tuberous sclerosis epilepsy model (Wong et al. 2003). Finally, Guo et al. (2010) observed decreased GLAST but unaffected GLT1 expression in the hippocampus of spontaneously epileptic rats.

Taken together, the data described so far indicate that glutamate uptake by astrocytes plays a crucial role in protecting neurons from hyperexcitability and excitotoxicity. However, whether this mechanism is disturbed in epilepsy is still under investigation.

8.5.3 Regulation of GS in Epilepsy

In the CNS, GS is predominantly expressed by astrocytes where it converts glutamate and ammonia to glutamine. Impaired GS activity has been hypothesized to play a crucial role in the pathogenesis of MTLE (Eid et al. 2013b). This hypothesis is supported by the following observations: (i) unilateral intrahippocampal infusion with the GS inhibitor methionine sulfoximine causes recurrent seizures and neuropathological changes similar to human MTLE (Eid et al. 2008a; Wang et al. 2009; Perez et al. 2012); (ii) reduced GS protein and enzyme activity have been found in MTLE-HS patients (Fig. 8.4) (Eid et al. 2004; van der Hel et al. 2005); interestingly, in a recent study no reduction of GS mRNA could be found in HS in the CA1 region, suggesting posttranscriptional modification of GS in epilepsy (Eid et al. 2013a); and (iii) mutations in the GS encoding gene, *GLUL*, are associated with reduced GS activity and epileptic seizures (Haberle et al. 2005, 2006, 2011). One argument against a causative role of GS dysfunction in epileptogenesis, however, arises from a study performed in a kainate model (Hammer et al. 2008). The authors demonstrated that although GS protein level was reduced during the chronic phase (confirming the findings in human tissue), increased GS levels were found in the latent period (prior to seizure onset). The mechanistic link between GS downregulation and seizure development is provided by the assumption that GS deficiency and the resulting decrease in glutamate to glutamine conversion causes intracellular glutamate accumulation. This accumulation, in turn, slows down glutamate uptake, leading to increased glutamate levels in the ECS (Coulter and Eid 2012; Eid et al. 2013b). Support for this view emerges from recent work showing that GS inhibition causes indeed glutamate accumulation in hippocampal astrocytes (Perez et al. 2012).

The glutamate-glutamine cycle is essential for replenishing the neurotransmitter pool and maintenance of synaptic activity. Interruption of the cycle through GS

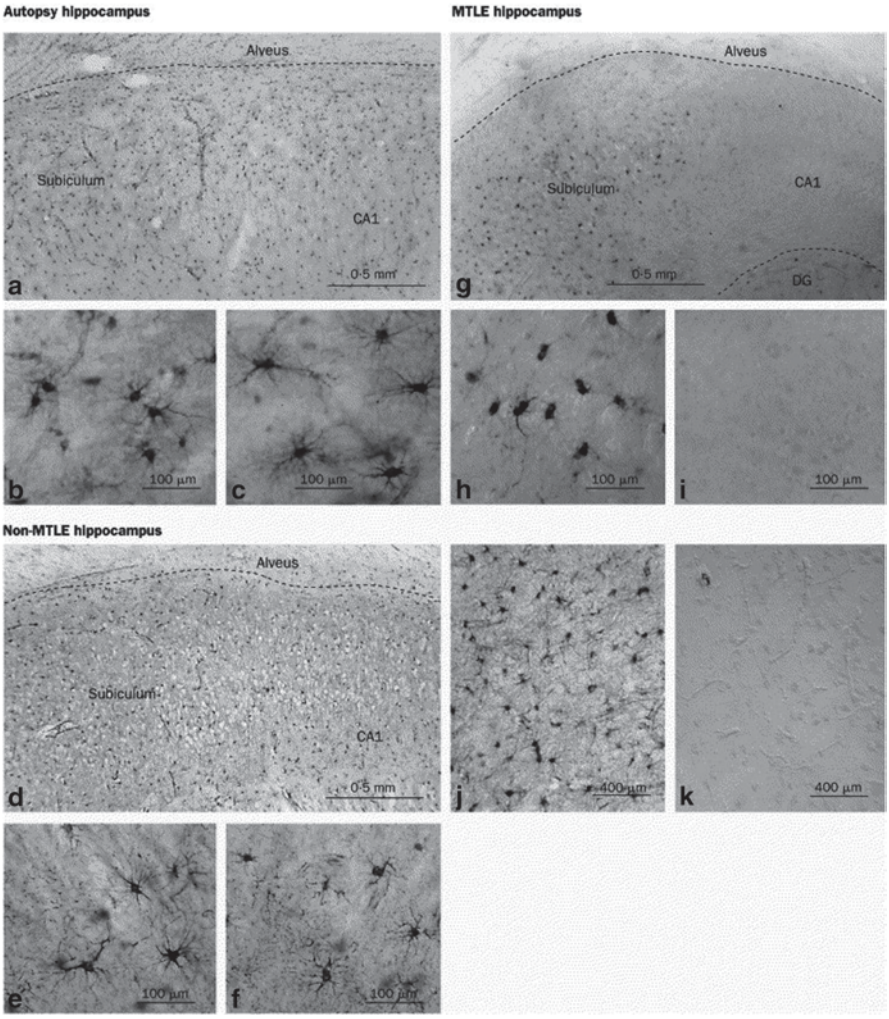

Fig. 8.4 Decreased GS immunoreactivity in the CA1 region of MTLE patients. There is dense and even distribution of GS-positive cells in the subiculum and CA1 region of autopsy (**a**) and non-MTLE hippocampi (**d**). High-power fields of subiculum in autopsy (**b**) and non-MTLE (**e**) hippocampi show that staining is confined to astrocytes. High-power fields of area CA1 in autopsy (**c**) and non-MTLE (**f**) hippocampi also show many GS-positive astrocytes. In MTLE hippocampus (**g**), there are many GS-positive cells in the subiculum but area CA1 is severely deficient in GS staining. High-power view of the subiculum in G (**h**) confirms presence of staining in astrocytes, which have fewer processes than GS-positive astrocytes in the corresponding areas of autopsy (**b**) and non-MTLE hippocampi (**e**). High-power view of area CA1 in G (**i**) confirms lack of GS staining in this region. Specificity controls with GS antiserum (**j**) and preimmune serum (**k**) on adjacent sections of the non-MTLE hippocampus shown in **d**–**f** reveal no staining in **k**. *DG* dentate gyrus. (Modified from Eid et al. (2004), reproduced with permission)

inhibition impairs inhibitory, i.e.γ-aminobutyric acid (GABA)-ergic transmission (Liang et al. 2006), but had little effect on excitatory (glutamatergic) synaptic function (Kam and Nicoll 2007). This phenomenon as well as its consequences on network excitability has been studied in detail in an *in vitro* model of astrocytic gliosis (Ortinski et al. 2010). In this study, virus-induced gliosis in the hippocampus caused downregulation of GS expression and deficit in inhibitory, but not excitatory synaptic transmission. Employing voltage-sensitive dye imaging the authors showed that these inhibitory deficits entail network hyperexcitability, which could partially be reversed by exogenously supplied glutamine. These data emphasize the importance of proper GS function for inhibitory neurotransmission and prevention of seizure generation (Ortinski et al. 2010).

8.6 Astrocyte Ca^{2+} Signaling and Gliotransmission in Epilepsy

8.6.1 Ca^{2+} Signaling

Already in the nineties of the past century it has been shown that astrocytes in culture (Cornell-Bell et al. 1990; Charles et al. 1991) and acute brain slices (Porter and McCarthy 1996) respond to glutamate with elevations in $[Ca^{2+}]_i$ which propagate through the astroglial network. Increased astrocytic $[Ca^{2+}]_i$, in turn, induced release of gliotransmitter, including glutamate, ATP, D-serine and GABA (Halassa et al. 2007; Crunelli and Carmignoto 2013). Hence, astrocytes not only sense, but also regulate synaptic transmission, neuronal excitability and plasticity. In human brain, bidirectional signaling between neurons and astrocytes has been demonstrated only recently (Navarrete et al. 2013). However, the mechanism by which astrocytes release gliotransmitter is still controversially discussed.

Evidence for the involvement of astrocytic Ca^{2+} waves and concomitant release of transmitters in epilepsy emerge from studies in brain slices and *in vivo,* demonstrating increased Ca^{2+} oscillations in astrocytes during epileptiform activity, which could be suppressed by anti-epileptic drugs (Tian et al. 2005; Fellin et al. 2006). In addition, metabotropic glutamate receptors, which mediate astrocytic Ca^{2+} signals, are up-regulated in experimental (Aronica et al. 2000; Ulas et al. 2000) and human (Tang and Lee 2001; Kandratavicius et al. 2013) epilepsy. Pilocarpine-induced SE caused long-lasting elevation in astrocytic $[Ca^{2+}]_i$ and the resulting glutamate release contributed to neuronal excitotoxicity (Ding et al. 2007).

8.6.2 Glutamate Release

Glutamate release from astrocytes synchronizes neuronal firing through activation of extrasynaptic NMDA receptors (Fellin et al. 2004; Angulo et al. 2004). Epileptic

discharges are characterized by excessive, hypersynchronous neuronal activity, leading to the suggestion that astrocytic glutamate release underlies the simultaneous activation of multiple neurons during such an event. Support for this view came from Tian et al. (2005) who studied paroxysmal depolarization shifts (PDSs) after inhibition of synaptic activity by tetrodotoxin (TTX) and Ca^{2+} channel blockers. PDSs, which underlie interictal activity, were largely insensitive to TTX but sensitive to α-amino-3-hydroxy-5-methyl-isoxazole propionate (AMPA) and N-methyl D-aspartate (NMDA) glutamate receptor antagonists, indicating that they were triggered by release of glutamate from extrasynaptic sources. Since photolysis of caged Ca^{2+} in individual astrocytes evoked local PDSs, the authors concluded that astrocytes are the primary source of glutamate in experimental seizure models (Tian et al. 2005). This conclusion was challenged by a subsequent study showing that astrocytic glutamate is not required for the initiation of epileptiform activity, but might have a modulatory role (Fellin et al. 2006). This view is supported by an elegant study of Gomez-Gonzalo et al. (2010), who combined patch clamp recording and Ca^{2+} imaging during *in vitro* seizures to assess the role of astrocytes in the generation of epileptiform activity. Their data revealed that ictal, but not interictal, discharges generate astrocytic $[Ca^{2+}]_i$ elevations (Fig. 8.5). In a new *in vitro* model of focal seizures induced by local application of NMDA in the presence of 4-aminopyridine and low Mg^{2+}, astrocytic Ca^{2+} signals preceded ictal discharges (Losi et al. 2010). These early Ca^{2+} signals appeared to have a causative role in the generation of focal ictal discharges, since their inhibition prevented NMDA-stimulated ictal discharges, while their stimulation enhanced discharges. In contrast to the findings by Tian et al. (2005), no association between $[Ca^{2+}]_i$ changes in astrocytes and interictal events could be found in this study. The authors concluded that bidirectional signaling between neurons and astrocytes in hyperexcitable networks generate a recurrent excitatory loop that promotes focal seizures (Gomez-Gonzalo et al. 2010).

8.6.3 Astrocyte Release of ATP and Epilepsy

In addition to its role in propagating inter-astrocytic Ca^{2+} waves, ATP release from astrocytes directly modulates synaptic transmission (Kumaria et al. 2008). Extracellular ATP is rapidly hydrolyzed to adenosine (Zimmermann and Braun 1996). Adenosine, in turn, potently suppresses excitatory synaptic transmission through activation of presynaptic A1 receptors (A1Rs) (Pascual et al. 2005a; Fredholm et al. 2005), indicating an anticonvulsive role of astrocytic ATP release (see Sect. 8.7).

In addition, extracellular ATP may activate purinergic receptors, which can have both pro- and anticonvulsant consequences. For instance, Torres et al. (2012) reported that the decrease in $[Ca^{2+}]_o$ accompanying excitatory synaptic transmission triggers ATP release from astrocytes through Cx43 HCs that, in turn, enhances inhibitory transmission by activating P2Y1 receptors on interneurons. In contrast, ATP released through Panx1 channels aggravates seizures and prolongs SE (Santiago et al. 2011). Astrocytic ATP has been proposed to possess seizure-promoting properties through activation of postsynaptic P2X receptors. The consequential

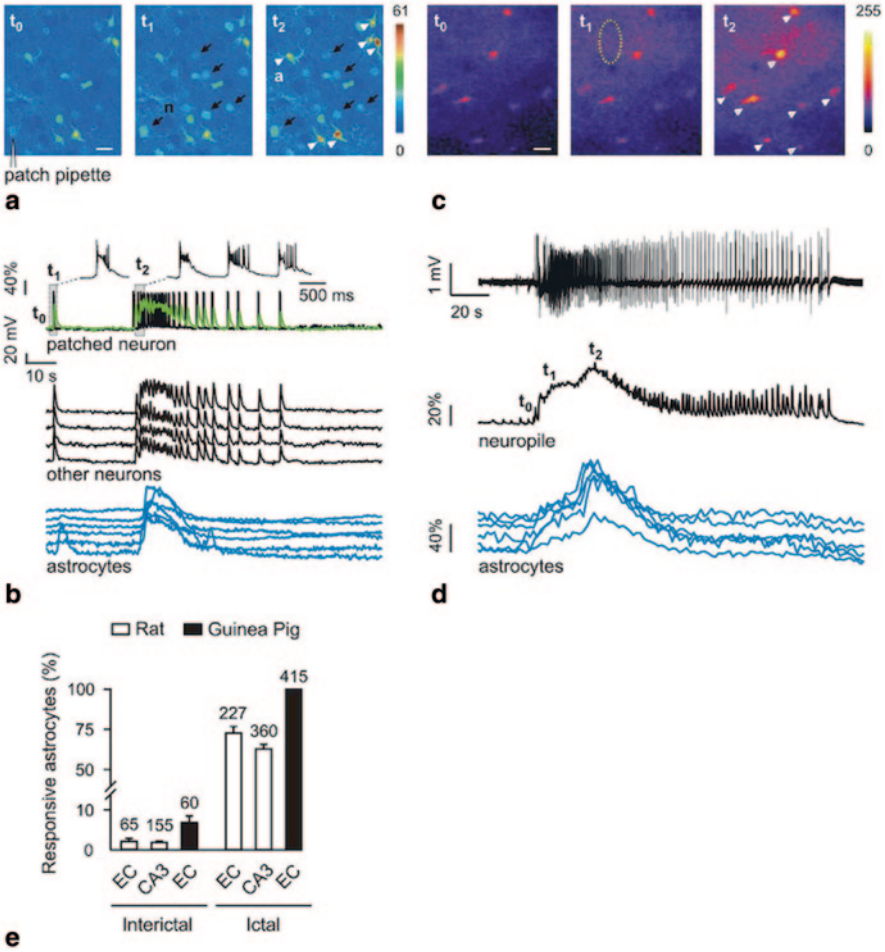

Fig. 8.5 Astrocytes respond with Ca^{2+} elevations to ictal, but not interictal, discharges. **a** Ca^{2+} changes at basal activity (t_0) in neurons (n, *black arrows*) and astrocytes (a, *white arrowheads*), during an interictal (t_1) or an ictal (t_2) event after perfusion with picrotoxin/zero Mg^{2+}. **b** Action potential bursts and Ca^{2+} change (*green trace*) of the patched neuron, and Ca^{2+} changes from other neurons and from astrocytes indicated in (**a**). Note the large Ca^{2+} rise in astrocytes upon ictal (t_2) but not interictal (t_1) events. **c** Ca^{2+} imaging in guinea pig entorhinal cortex before (t_0) and during (t_1 and t_2) ictal discharges induced by arterial perfusion with bicuculline. **d** Field potentials and Ca^{2+} changes from neuropil (*dashed oval* in **c**) and astrocytes (*arrowheads* in **c**) during ictal discharges. **e** Proportion of astrocytes activated during interictal and ictal events. Cell numbers are indicated above bars. (From Gomez-Gonzalo et al. (2010), reproduced with permission)

elevation in neuronal Ca^{2+} levels promotes the insertion of AMPA receptors and synaptic strength (Gordon et al. 2005).

Taken together, the role of gliotransmission in the pathophysiology of epilepsy is still unresolved. Clarification of the functional significance of the different

astrocyte-to-neuron signaling pathways represents an intriguing challenge and attracts increasing interest for developing new, anti-epileptogenic therapies.

8.7 Adenosine Dysfunction in Epilepsy

8.7.1 Role of Astrocyte-derived Adenosine in Epilepsy

The anticonvulsive action of adenosine has been demonstrated already three decades ago (Dunwiddie 1980; Lee et al. 1984; Dragunow et al. 1985). Since, various studies on experimental models and human epileptic tissue have confirmed and further elucidated these initial findings (Boison 2010, 2012). Extracellular adenosine levels rapidly rise during seizures, a process that probably mediates seizure termination and postictal suppression (During and Spencer 1992). Mice intracranially implanted with adenosine-releasing polymers, encapsulated cells or embryonic stem cells showed profound reduction of seizure activity in the kindling model (Boison et al. 1999, 2002; Huber et al. 2001; Li et al. 2007b). The anticonvulsive action of adenosine is mainly mediated via activation of G protein-coupled A_1Rs (Boison 2010, 2012). Consistently, A_1R agonists possess anticonvulsant and neuroprotective effects (Dunwiddie and Worth 1982; Barraco et al. 1984; Gouder et al. 2003; Li et al. 2013), while antagonists promote seizures and aggravate neuronal damage (Dunwiddie 1990; Ault et al. 1987; Avsar and Empson 2004; Vianna et al. 2005). Homozygous and heterozygous A_1R knockout mice exhibit spontaneous seizures in the CA3 area of the hippocampus (Li et al. 2007a). Furthermore, in the kainate model these animals displayed more severe SE and neuronal loss (Fedele et al. 2006). In human MTLE-HS (Glass et al. 1996) and rodent HS (Cremer et al. 2009; Aden et al. 2004) A_1Rs are downregulated.

Several studies have indicated that extracellular adenosine originates from hydrolyzed ATP released from astrocytes through Cx HCs, Panx channels (Kang et al. 2008; Santiago et al. 2011) or exocytosis (Pascual et al. 2005a). The latter study investigated the role of astrocytes in regulating synaptic transmission using transgenic mice, which overexpressed a dominant-negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor (dn-SNARE mice) specifically in astrocytes. In these mice adenosine-mediated heterosynaptic depression was absent, confirming the astrocytic origin of extracellular adenosine (Pascual et al. 2005b).

8.7.2 Role of Glial ADK in Epilepsy

The ambient adenosine level is controlled by the activity of the enzyme ADK, which is critically involved in adenosine metabolism by phosphorylating adenosine to 5′-AMP, and which in the adult brain is mainly expressed in astrocytes. Since cytoplasmic and extracellular adenosine levels are tightly balanced by nucleoside

transporters, even small changes in ADK activity can influence extracellular adenosine concentrations and consequently neuronal excitability (Boison 2010; Aronica et al. 2013). Overexpression of ADK was found in human MTLE-HS (Aronica et al. 2011) and in experimental epilepsy (Gouder et al. 2004; Aronica et al. 2011; Li et al. 2008, 2012). Interestingly, in the intrahippocampal kainate model, Gouder et al. (2004) observed a transient reduction of ADK immunoreactivity during the first 24 h post SE, but pronounced overexpression during the later stages of epileptogenesis. The authors speculated that the initial reduction of ADK and the resulting increase in extracellular adenosine may contribute to termination of SE, while the enhanced ADK expression may contribute to chronic seizures by decreasing ambient adenosine. In experimental focal epilepsy, astrogliosis, ADK overexpression and spontaneous recurrent seizures are tightly associated (Li et al. 2008, 2007a, 2012).

In line with the expression studies, pharmacological inhibition of ADK potently inhibited seizures in experimental epilepsy (Kowaluk and Jarvis 2000; Gouder et al. 2004). Moreover, transgenic or viral overexpression of ADK in mice resulted in spontaneous recurrent hippocampal seizures, while viral knockdown of ADK prevented seizures. Since ADK overexpression was not accompanied by astrogliosis, these studies indicate that ADK overexpression is sufficient to trigger seizures and cause chronic seizure activity (Li et al. 2007a, 2008; Theofilas et al. 2011; Boison 2010, 2012; Aronica et al. 2013).

These above findings gave rise to the ADK hypothesis of epileptogenesis, which considers this enzyme both as a diagnostic marker as well as a potential therapeutic target to prevent epileptogenesis.

8.8 Astrocyte Immune Responses and Epilepsy

8.8.1 Astrocyte Changes Induced by Brain Inflammation

Brain inflammation has been implicated in the pathogenesis of epilepsy. Increased levels of inflammatory mediators, loss of blood-brain-barrier integrity and mono/lymphocyte infiltration were found in sclerotic tissue from MTLE patients as well as in animal models of TLE. There is growing evidence that inflammation is not only a consequence but also cause of epilepsy (Vezzani et al. 2011a). This assumption is supported by the following set of findings. (i) Cytokines like interleukin-1beta (IL-1β) and damage associated molecular pattern (DAMPs) like high mobility group box 1 (HMGB1) promote seizures in experimental epilepsy (Maroso et al. 2011). Preapplication of IL-1β or HMGB1 prolongs the duration of seizures induced by chemoconvulsant drugs (kainate, $GABA_A$ receptor antagonist bicuculline), while preapplication or overexpression of the corresponding antagonists or substances which inhibit IL-1β production attenuate seizure activity. Moreover, transgenic mice lacking functional receptors for the respective cytokines and

DAMPs displayed reduced susceptibility for seizures (Vezzani et al. 2000; Maroso et al. 2010). (ii) Seizures arising during fever (febrile seizures) are the most frequent type of seizures in children (Dube et al. 2012). (iii) Experimental induction of fever by lipopolysaccharide (LPS) injection or hyperthermia results in long-term enhancement of seizure susceptibility (Dube et al. 2012; Galic et al. 2008; Auvin et al. 2009, 2010). However, the mechanism linking inflammation and epilepsy is still unclear. Proinflammatory cytokines enhance neuronal excitability by directly modifying the function of neuronal voltage- and receptor-gated ion channels (Vezzani et al. 2012). However, IL-1β and other cytokines may also indirectly influence neuronal excitability by altering astrocyte function. For instance, in culture or acute rat slices, IL-1β and tumor necrosis factor α (TNFα) inhibit glutamate reuptake and increase glial glutamate release (Bezzi et al. 2001; Hu et al. 2000; Ye and Sontheimer 1996), which can be expected to produce hyperactivity. Furthermore, in cultured astrocytes cytokines inhibit Cx43 GJ channels, and open Cx43 HCs (Meme et al. 2006; Retamal et al. 2007). Intriguingly, cytokine-induced uncoupling in culture could be rescued by treatment with the anti-epileptic drug levetiracetam (Keppra®) (Haghikia et al. 2008). Whether astrocytic uncoupling and/or Cx HC activation is pro- or anticonvulsive needs to be clarified (see Sects. 8.3.2 and 3.3). Moreover, IL-1β and LPS increase ADK expression in human astrocyte cultures (Aronica et al. 2011). As described above (Sect. 8.7.2), ADK overexpression is sufficient to trigger seizures. Of note, glial Kir4.1 expression in culture is down-regulated after exposure to IL-1β (Zurolo et al. 2012). Given the essential role of Kir4.1 in K^+ buffering (Sect. 8.2), the consequence of this down-regulation on neuronal excitability seems to be evident.

Collectively, these findings demonstrate that proinflammatory mediators cause several dysfunctions in astrocytes, which individually or in concert provoke neuronal hyperexcitability.

8.8.2 Involvement of Astrocytes in Brain Inflammation

Astrocytes contribute to inflammation in the CNS by producing a variety of chemokines and cytokines (Aronica et al. 2012). Cytokines like IL-1β and TNFα are overexpressed by astrocytes in both human and experimental epilepsy (Vezzani et al. 2008). Importantly, during the latent period IL-1β was exclusively expressed by astrocytes in a rat model of epilepsy. In chronic experimental and human epilepsy about 10-fold more IL-1β-positive astrocytes than microglia were observed, indicating that astrocytes are the main source of IL-1β in the epileptic brain (Ravizza et al. 2008).

An important role in the astrocyte immune response has been suggested for the IL-1 receptor/toll-like receptor (IL-1R/TLR) superfamily (Maroso et al. 2010, 2011). In the human brain IL-1R and TLR4 are expressed at low levels in astrocytes under control conditions and are up-regulated in the sclerotic hippocampus from MTLE patients (Ravizza et al. 2008; Maroso et al. 2010). In the absence of

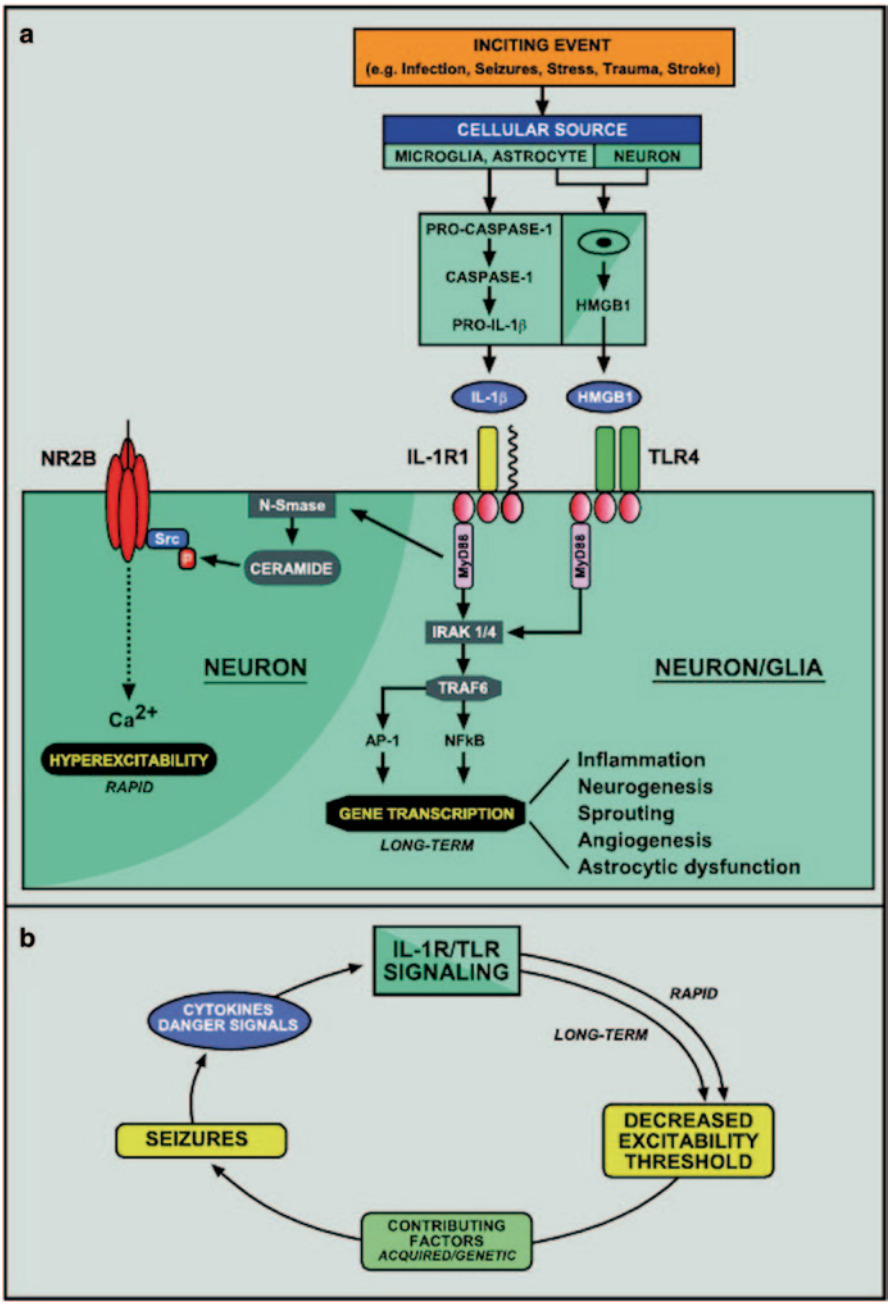

Fig. 8.6 Pathophysiological cascade mediated by IL-1R/TLR signaling in epilepsy. **a** Inciting events, initiated by local injuries or peripherally following infections, lead to activation of microglia, astrocytes and neurons. These cells release proinfammatory cytokines such as IL-1β, and danger signals such as HMGB1, thereby eliciting a cascade of inflammatory events in the target cells (i.e. neurons and glia) via activation of IL-1R1 and TLR4. This rapidly increases neuronal

pathogens, TLR signaling can be activated by DAMPs released by injured or dying cells. One member of the DAMP protein family, HMGB1, is released by cultured astrocytes upon IL-1β stimulation, and its nuclear to cytoplasmic translocation was observed in human and murine epileptic hippocampus (Maroso et al. 2010). Activation of IL-1R/TLR signaling induced Src kinase-dependent phosphorylation of the GluN2B subunit of the NMDA receptors, resulting in higher NMDA-dependent Ca^{2+} influx and neuronal hyperactivity (Vezzani et al. 2011b; Maroso et al. 2010). In addition, IL-1R/TLR signaling triggers, via nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) activation, transcription of several genes encoding downstream mediators of inflammation, like IL-6, TNFα or cyclooxygenase-2, which may further promote seizures (Vezzani et al. 2011b). Indeed, overexpression of NF-κB has been observed in the human sclerotic hippocampus (Crespel et al. 2002).

These findings led to a model for the involvement of the IL-1R/TLR axis in epileptogenesis (Fig. 8.6). An inciting event, like infection, seizures or stroke, leads to cellular stress and/or injury and release of IL-1β (from microglia and astrocytes) and HMGB1 (from astrocytes and neurons) from their constitutive endogenous pools. Activation of IL-1R/TLR signaling in neurons and astrocytes by the released molecules results in several cellular changes (such as GluN2B phosphorylation), which contribute to the generation of the first seizure. Seizures, in turn, induce *de novo* synthesis of IL-1β, HMGB1 and other proinflammatory mediators, which contribute to seizure recurrence (Vezzani et al. 2011b; Maroso et al. 2010). Thus, IL-1R/TLR signaling might represent promising targets for antiepileptic treatments.

Conclusions

The fact that astrocytes are now recognized as communication partners of neurons and do not merely represent "brain glue" has rekindled the question of the role of these cells in neurological disorders such as epilepsy. Compelling evidence is emerging demonstrating severe dysfunction of astrocytes in human and experimental epilepsy. However, several important questions still remain open. First, it is still unclear whether the reported alterations in astrocytes are causative of the condition or rather represent a compensatory phenomenon. Second, difficulties arise from the fact that the term "astrocyte" covers a heterogeneous group of cells, which complicates comparison of published work. Indeed, it is becoming increasingly clear that the molecular, functional and morphological properties of astrocytes do not

NMDA receptor Ca^{2+} conductance via ceramide/Src mediated phosphorylation of the GluN2B (NR2B) subunit, leading to hyperexcitability. Long-term decrease in seizure threshold results from activating transcription of genes, contributing to molecular and cellular changes involved in epileptogenesis and perpetuating inflammation. **b** Inflammation due to activation of IL1R/TLR signaling contributes to seizure generation by decreasing the threshold of neuronal excitability. Seizure recurrence, in turn, activates further inflammation, thereby establishing a vicious circle of events that contributes to the development of epilepsy. (From Vezzani et al. (2011b), reproduced with permission)

only vary across brain areas but even within a given subregion. Nevertheless, the combination of molecular genetics with functional approaches will help clarifying the specific roles of astrocytes in epilepsy and enable developing novel therapeutic approaches to better treat this disorder.

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