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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