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Editorial

Glial cells as primary therapeutic targets for epilepsy

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ABSTRACT

Neurons have been the natural focus of discussion for most of the history of research on seizures and epilepsy. Simply stated, epilepsy is a disease of sporadic, progressive disruption of neuronal activity. Thus causes and therapies for epilepsy have been naturally aimed at the obvious manifestation of disease: neuronal dysfunction. However, over the last two decades a new view is beginning to emerge that is defining the dependence of neuronal function and seizure susceptibility on glia. This view changes the definition of epilepsy as a disease of neurons to a disease of a heterogeneous neuronal-glial network. This new glial focus is suggesting new opportunities to treat the nearly 1/3 of individuals who do not respond to traditional antiepileptic drug (AEDs) therapies as well as suggesting ways to reduce the many unwanted side effects of AEDs.

Over the last two decades, several lines of evidence suggest 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). Neurons alone cannot sustain brain's multiple physiological functions. Glia play essential roles. For example, astrocytes play an established role in removal of glutamate at synapses, neuronal path finding, and the sequestration and redistribution of K^+ during neural activity (Ransom et al., 2003). Microglia are the resident tissue macrophage of the CNS. As such these cells play dual roles surveying CNS homeostasis during health and cross-regulating astrocytic functions following brain injury and infection (Carson et al., 2006). Thus it should not be unexpected that glial cells can play triggering roles in seizure susceptibility and the development of epilepsy (Binder et al., 2012a; Binder and Steinhäuser, 2006; Clasadonte and Haydon, 2012; Friedman et al., 2009; Hsu et al., 2007; Seifert et al., 2010, 2006; Tian et al., 2005). For example, direct stimulation of astrocytes leads to prolonged neuronal depolarization and epileptiform discharges (Tian et al., 2005). Gilial 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., 2012a; 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. Until recently these morphologic changes were often viewed just as biomarkers of reactive gliosis responding to neuronal dysfunction. However, these morphologic changes may directly contribute to increased neuronal excitability and the development of epilepsy. Morphologic changes may be indicative of dysregulation of water and ion channel expression, alterations in secretion of neuroactive molecules, and increased activation of inflammatory pathways (Binder et al., 2012a; 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).

The many changes that occur in glial cells that may be responsible for contributing to epileptogenesis open up new therapeutic targets for drug development and more broadly open up new understanding of epilepsy as a "network" disease. An overview of the glial cell changes in epilepsy is provided by Jacqueline Hubbard, Mike Hsu, Todd Fiacco and Devin Binder in this Special Issue.

Related to the development of antiepileptic drugs, new approaches, mechanisms and targets are sorely needed. 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

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phenytoin or carbamazepine, hormonal forms of contraception are affected and the efficacy of oral contraceptive cannot be guaranteed (Crawford, 2005), thus complicating family planning. Finally, AEDs are associated with a number of adverse effects including mood alteration, suicidality, severe mucocutaneous reactions, hepatotoxic effects, decreased bone mineral density, and weight management difficulties among others, which often leads to treatment failure (Perucca and Gilliam, 2012).

Thus, new "glial" targets for antiepileptic drugs may have increased efficacy as well as decreased side effects due to lack of effect on neuronal targets. The ideal drug would prevent the development of epilepsy (*e.g.* after head injury or status epilepticus) and/or inhibit established seizures without causing significant side effects related to chronic depression of normal brain activity. Thus a "glial" drug might target specific epilepsy-related pathological changes in glia with the goal of targeting disease while not altering normal neuronal synaptic transmission.

In this regard, several of the studies outlined in this Special Issue warrant mention. Tore Eid, Nathan Tu, Tih-Shih Lee and James Lai review studies of the important astrocytic enzyme glutamine synthetase, its changes during epilepsy and therapeutic implications. Meredith Gibbons, Roy Smeal, D.K. Takahashi, Jay Vargas and Karen Wilcox examine the contributions of astrocytes to epileptogenesis following status epilepticus and discuss opportunities for preventive therapy. Peter Bedner and Christian Steinhäuser discuss the role of alterations in Kir and gap junction channels in temporal lobe epilepsy. Eleonora Aronica, Ursula Sandau, Anand Iyer and Detlev Boison highlight the role of changes in glial adenosine kinase in the epileptic brain. Each of these groups of studies has generated specific new targets for potentially new glial-specific antiepileptic drugs.

It is also becoming clear that changes in glial cells may contribute to not only the generation of seizures but also to epilepsy-related neuropsychological deficits. While this field is still in its infancy, it is certainly possible that pathological glial alterations, in particular in the hippocampus, may contribute to epilepsy-associated cognitive deficits. Cognitive impairment is very important because patients with temporal lobe epilepsy have many alterations in cognitive function and in particular hippocampal-dependent tasks such as spatial memory (Amlerova et al., 2013; Bell et al., 2011; Brooks-Kayal et al., 2013; Chin and Scharfman, 2013). In this Special Issue, Binder and Scharfman highlight the unanticipated role of the astrocyte water channel aquaporin-4 (AQP4) in synaptic plasticity and object placement memory. Interestingly, AQP4 deletion had a specific effect on long-term synaptic transmission (LTP) induced by theta-burst stimulation (TBS) but did not impair basal synaptic transmission. Given that expression of AQP4 is restricted to glia, the results support previous reports that glia play a role in LTP (Bains and Oliet, 2007; Djukic et al., 2007; Filosa et al., 2009; Ikeda et al., 2007; Todd et al., 2006; Volterra and Steinhauser, 2004), and suggest a new mechanism for the contribution of glia to activity-dependent plasticity.

Restoration of water and ion homeostasis represents a novel concept for treatment in addition to standard concepts of neuroprotection. In the context of epilepsy, changes in glial water and potassium homeostasis have been described in multiple animal models and human tissue studies (Binder et al., 2012a). In particular, marked downregulation of AQP4 has been observed following status epilepticus in animal models of epilepsy (Lee et al., 2012) as well as in human tissue resected from patients with epilepsy (Eid et al., 2005). Such downregulation of AQP4 may not only lead to increased neural excitability due to abnormalities of water and potassium homeostasis but may also lead directly to abnormalities in synaptic transmission (both LTP and LTD). This provides a potential explanation for the way that astrocytic changes in epilepsy contribute not only to seizures but also to known cognitive deficits.

Furthermore, new studies outlined in this Special Issue deepen understanding of epilepsy as truly a "network" disease. It used to be thought that the "epileptic network" was a network of neurons (McCormick and Contreras, 2001), but it is now clear that not only neurons but the interaction of neurons, astrocytes, microglia, blood vessels, and even blood-derived molecules contribute to the establishment and perpetuation of the epileptic state. Giuseppe Bertini, Placido Bramanti, Gabriela Constantin, Michele Pellitteri, Beatrice Radu, Mihai Radu and Paolo Fabene discuss the new concept of the "neurovascular unit" or NVU and how changes in the NVU may influence seizures and epilepsy. Naturally, this realization and further studies could lead to entirely novel and nontraditional antiepileptic drug targets.

Part of the challenge of studying epilepsy has been in the broad variety of epileptic syndromes and also that epilepsy can be a "final common pathway" of diverse brain disorders. Nevertheless, the glial contribution to distinct epileptic syndromes has been expanding. Most of the studies outlined above related to the glial changes in common models of temporal lobe epilepsy, the most common single disorder leading to medically-intractable epilepsy. Recent studies have indicated a glial contribution to tumor-associated epilepsy as well. In this Special Issue, Susan Buckingham and Stefanie Robel explain novel findings about glial-derived glutamate and tumor-associated epilepsy, highlighting the role of glial cell dysfunction in the peritumoral environment. One way of determining commonalities of glial "dysfunction" that may contribute to a hyperexcitable state in epileptic tissue is to attempt to identify glial biomarkers. If such biomarkers can be validated then they may serve as proxies for glial involvement in various forms of epilepsy. In this Special Issue, Andre Obenaus reviews recent neuroimaging studies of biomarkers for epilepsy and their relevance to changes in glial cells.

In summary, the revolution in glioscience is starting to illuminate the field of epilepsy. New targets for antiepileptic drugs and new concepts of what constitutes the epileptic "network" have already been generated from many laboratories and investigators. It is clear that with deeper understanding of glial biology comes deeper understanding of the glial contribution to disease pathophysiology. In the field of epilepsy research, we must harness this revolution in glioscience to move from new targets to new therapy.

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