Reactive Astrogliosis in Epilepsy - Passive Bystanders no more

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Introduction

Temporal lobe epilepsy (TLE) is a neurological disorder that is characterized by spontaneous, recurrent seizures and can be associated with reactive astrogliosis (also known as astrogliosis). This is an adaptive process that consists of alterations in structure and biochemistry of astrocytes and is important for tissue repair and regulation of inflammation. Anti-epileptic drugs (AEDs) used to manage TLE can be associated with refractoriness and substantial side-effects. Most AEDs act through mechanisms that primarily involve neurons; hence, examining the role of reactive astrogliosis in epilepsy could lead to development of novel therapies for epilepsy. The exact role of reactive astrogliosis in epilepsy is not well understood, as experiments suggest both potential pro- and anti-epileptogenic effects [1,2]. Given that epilepsy can be associated with neurodegeneration, mossy fiber sprouting and changes in receptor and neurotransmitter function, examining the specific role of reactive astrogliosis in epilepsy has been fraught with difficulties. Previously, a transgenic mouse line was generated [3] where deletion of β1-integrin preferentially in radial glia caused reactive astrogliosis marked by hypertrophy and upregulation of astrocyte-specific markers. Using this transgenic mouse line, in the current Journal of Neuroscience study [4], the authors examined whether reactive astrogliosis by itself was sufficient to cause epilepsy, and what the underlying mechanisms would be.

In all experiments, control mice were compared to those with reactive astrogliosis caused by deletion of β1-integrin in radial glia (‘β1-/- mice’). First, reactive astrogliosis was qualitatively and quantitatively confirmed in the cortex of β1-/- mice at various ages. β1-/- mice also had microglial activation; this could be a consequence of reactive astrogliosis as the authors suggest, but could be an independent process as well (http://www.jneurosci.org/content/35/B/3330/F1.expansion.html). EEG analysis revealed that a subset of β1-/- mice exhibited spontaneous seizures; interestingly, there was a correlation between levels of GFAP and seizure frequency. Interictal spikes (IIS) - the hallmark of an epileptiform activity in β1-/- mice was seen. Examination of action potentials in response to current injection and input output (I/O) curves also showed that Layer II/III pyramidal cells in the cortex of β1-/- mice were more excitable than slices from control mice. But how does one know that these results are specific to astrocytes? To address this, the authors used mice where β1-integrin was deleted from neurons instead of radial glia (β1-/- Nex::Cre mice) and found that these mice did not exhibit hyperexcitability in response to Mg2+-free aCSF (artificial cerebrospinal fluid: http://www.jneurosci.org/content/35/B/3330/F4.expansion.html). However, examining whether β1-/- Nex::Cre mice exhibit spontaneous seizures would have been quite informative.

To explore possible reasons underlying epilepsy and in vitro epileptiform activity in β1-/- mice, the authors examined glutamate uptake and homeostasis of K+ and Cl- ions. Astrocytes play a critical role in tightly regulating K+ homeostasis in the normal brain; indeed increasing K+ concentration is an in vitro model of inducing epileptiform activity. Kir4.1 channels mediate K+ conductance and conditional knockout of Kir4.1 channels in astrocytes is associated with greater propensity to seizures [5]. In line with this, tissue from people with hippocampal sclerosis was found to have abnormally high level of extracellular K+ [6]. In the current study, K+ homeostasis in β1-/- mice was studied by recording from astrocytes (http://www.jneurosci.org/content/35/B/3330/F5.expansion.html), and parameters of K+ homeostasis showed modest deficiencies in mice with reactive astrogliosis.

Astrocytes are the primary cell type responsible for glutamate uptake [7] - a single astrocyte can release enough glutamate to depolarize 2-4 adjacent neurons. An increased intracellular glutamate in the hippocampus has been observed in human
epileptic tissue [8]. In β1−/− mice, though there were few changes in glutamate transporters, glutamate uptake was vastly decreased, suggesting increased extracellular glutamate as a contributor of hyperexcitability. Glutamine synthetase (GS) - an enzyme necessary for degradation of glutamate into glutamine and for providing precursors for the production of GABA - was reduced in β1−/− mice [http://www.jneurosci.org/content/35/8/3330/F6.expansion.html]. After exploring excitatory neurotransmission, the authors examined the inhibitory system, as the presence of epileptiform activity could represent an imbalance in GABAergic neurotransmission. GABAergic transmission is regulated by two Cl co-transporters NKCC1 and KCC2, and alterations in the ratio of these co-transporters so as to confer GABA a depolarizing effect have been shown in neuronal development and epilepsy [9]. Similarly, in this study, the authors found increased NKCC1 [http://www.jneurosci.org/content/35/8/3330/F8.expansion.html]. Although not examined here, the electrophysiological correlate of this alteration in Cl co-transporter ratio would be interesting to see. Administration of bumetanide - a drug that blocks NKCC1 showed a reversal in the seizure phenotype in a subset of β1−/− mice [http://www.jneurosci.org/content/35/8/3330/F8.expansion.html]. In summary, this is the first study to show that global reactive astrogliosis is sufficient to cause seizures, at least partly due to aberrations in glutamate uptake and Cl co-transporters. This was found in the absence of blood brain barrier (BBB) compensation, which is important because BBB breach can cause or exacerbate seizures by itself.

Reactive astrogliosis in this study was induced by deleting β1-integrin from radial glia at birth. Since radial glia are critical for neuronal migration, examining neuronal migration in β1−/− mice could have helped rule out effects of mismigration on seizures. This is relevant because neuronal mismigration on its own can contribute to seizures e.g. seizures seen in lissencephaly, and due to ectopic granule cells in the hippocampus. Reactive astrogliosis is a hallmark of hippocampal sclerosis - a process typically seen in mesial TLE. In this study, the authors studied the cortex, but investigating the temporal lobe would be quite instructive. This study leads us to ask the question of what would happen if reactive astrogliosis were induced only in a certain area or circuitry of the brain, as opposed to the entire brain as it was done here. Not all mice with reactive astrogliosis showed epilepsy, and only a subset of mice administered bumetanide showed reversal of the seizure phenotype. Why this is the case is not known; however, there is some relevance to the clinical realm, as not everyone with traumatic brain injury develops epilepsy. This study also explains why resecting the sclerotic hippocampus - an area that is invaded by glia - provides seizure reduction. Another question that this study raises is whether stopping reactive astrogliosis could then cause hyperexcitability and perhaps seizures. A recent study [11] compared tissue from patients with hippocampal sclerosis (HS) to those without HS, and found that all HS patients showed an uncoupling of astrocytes. In a mouse model of epilepsy, administration of inflammatory mediators was able to cause profound astrocyte uncoupling, which was observed as early as 4 hours post-status epilepticus; hence, early astrocyte uncoupling could possibly predict who with traumatic brain injury develops epilepsy later on. In summary, this journal of Neuroscience [4] study provides data suggesting that epilepsy could be viewed as a glial - and not neuronal - dysfunction. Hence, targeting glia could lead to better therapies for epilepsy and associated comorbidities.

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