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Review

Turning down the volume: Astrocyte volume change in the generation and termination of epileptic seizures

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ABSTRACT

Approximately 1% of the global population suffers from epilepsy, a class of disorders characterized by recurrent and unpredictable seizures. Of these cases roughly one-third are refractory to current antiepileptic drugs, which typically target neuronal excitability directly. The events leading to seizure generation and epileptogenesis remain largely unknown, hindering development of new treatments. Some recent experimental models of epilepsy have provided compelling evidence that glial cells, especially astrocytes, could be central to seizure development. One of the proposed mechanisms for astrocyte involvement in seizures is astrocyte swelling, which may promote pathological neuronal firing and synchrony through reduction of the extracellular space and elevated glutamate concentrations. In this review, we discuss the common conditions under which astrocytes swell, the resultant effects on neural excitability, and how seizure development may ultimately be influenced by these effects.

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1. Introduction: epilepsy models and astrocytes

Epilepsy is one of the most common neurological disorders in the world, affecting roughly 65 million people worldwide (Hirtz et al., 2007; Ngugi et al., 2010) and encompassing over 40 different seizure disorders (Berg et al., 2010). Current antiepileptic drugs (AEDs) are inadequate, as most produce negative side effects on cognition (Aldenkamp, 2001; Aldenkamp et al., 2003; Lagae, 2006) and fail to control seizures in approximately 30% of patients (Brodie et al., 2012; Brodie and Dichter, 1996; Kwan and Brodie, 2000). Those with uncontrolled seizures suffer high rates of mortality (Devinsky, 2004a; Laxer et al., 2014; Park et al., 2015) and comorbid neurological disorders (Boylan et al., 2004; Devinsky, 2004b; Kwan and Brodie, 2001). Research on drug-resistant forms of epilepsy, such as temporal lobe epilepsy (TLE), has historically focused almost exclusively on acute and/or long-term changes in neuronal firing and excitability. This approach, however, does not account for non-neuronal cells, which comprise ~50%

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of the brain (Azevedo et al., 2009). A growing body of work suggests that astrocytes, microglia and other glial cell types may play essential roles in the pathology of epilepsy.

Many recently developed epilepsy models have been built upon manipulations of glial cells, especially astrocytes. Astrocytes are a particularly attractive target for epilepsy given their control over neuronal excitability (Hubbard et al., 2013; Wetherington et al., 2008). Key changes contributing to hyperexcitability in epileptic tissue can be directly linked to changes in astrocyte function. For example, extracellular glutamate levels are excessively high in epileptic tissue (Cavus et al., 2005; During and Spencer, 1993), resulting in part from impaired astrocyte glutamate metabolism (Eid et al., 2004) and possibly glutamate transport (Proper et al., 2002). Broberg et al. (2008) found that seizures could be reliably induced by focal intracerebral injection of the astrocyte metabolic inhibitor fluorocitrate (FC). Similarly, the astrocytic enzyme glutamine synthetase (which recycles glutamate into glutamine for transport back to neurons) has been targeted with methionine sulfoximine (MSO) infusions into the hippocampus, producing acute status epilepticus (SE, a prolonged seizure) and gradual development of spontaneous recurrent seizures (SRS) (Albright et al., 2016; Eid et al., 2008; Wang et al., 2009). Serum albumin, which can sometimes enter the brain through a compromised blood brain barrier (BBB) in epileptic tissue, was found to directly bind astrocytic TGF-β receptors and induce reactive gliosis followed by seizures in rats (Ivens et al., 2007; Seiffert et al., 2004). Genetic deletion of β-integrin from astrocytes, which produces reactive gliosis without BBB disruption (Robel et al., 2009) was also sufficient to produce SRS within the first six weeks of life (Robel et al., 2015), indicating reactive gliosis alone may be sufficient for epileptogenesis. These and other findings suggest that astrocytes may be actively involved in the development of recurrent seizures.

A common underlying factor in many models of epilepsy is astrocyte swelling. In the following sections, we will discuss the evidence pointing to a significant role for astrocyte swelling in the development and maintenance of seizures, including the specific observations of tissue volume changes in seizures, physiological and pathological factors affecting astrocyte volume, and finally the consequences of astrocyte swelling in the context of hyperexcitable tissue.

2. Tissue swelling and seizures

Space within the brain is both limited and tightly regulated, and neuronal function depends upon the careful balancing of water, ions and neurotransmitter concentrations in the extracellular space (ECS). Accordingly, losing this balance can be a medical emergency. Acute plasma hypoosmolality, often due to low serum Na^+ levels (hyponatremia) has been known for nearly a century to cause direct swelling of the brain, muscle spasms, generalized seizures, coma or even death (Andrew, 1991; Castilla-Guerra et al., 2006; Rowntree, 1926). The effects of plasma hypoosmolality are most directly induced by accidental overhydration, as might occur in psychogenic polydipsia (compulsive water drinking, a symptom occurring in some cases of schizophrenia), or rapid water intake following dehydration. Multiple disorders which can acutely reduce plasma osmolality are also associated with seizures, including syndrome of inappropriate ADH secretion (SIADH), dialysis disequilibrium syndrome, transurethral resection of the prostate (TURP) syndrome and diabetes mellitus (Andrew, 1991). Ironically, certain antiepileptic drugs may even result in hyponatremia, although generally asymptomatic (Berghuis et al., 2016; Kim et al., 2014; Lu and Wang, 2017; Shepshelovich et al., 2017). Reductions of brain interstitial osmolarity can lead to "cellular" edema (occasionally sub-classified as "osmotic" edema), as water flows into neural cells causing them to swell (Kimelberg, 1995; Thrane et al., 2014). This in turn shrinks the ECS (Andrew and MacVicar, 1994; Chebabo et al., 1995b; Kilb et al., 2006) which is a critical regulator of neuronal excitability. In addition to increasing effective concentrations of extracellular ions and neurotransmitters, ECS reductions bring neurons closer together and increase nonsynaptic, neuron-to-neuron electrical field (ephaptic) interactions, resulting in more synchronous firing and bursting activity (Andrew et al., 1989; Ballyk et al., 1991; Dudek et al., 1986). Unsurprisingly, neuronal excitability is highly sensitive to extracellular shifts in osmolarity (Azouz et al., 1997; Chebabo et al., 1995a; Huang et al., 1997; Lauderdale et al., 2015). Multiple studies have demonstrated that seizures and other epileptiform activity can either be induced by lowering extracellular osmolarity, or abolished by increasing extracellular osmolarity (Dudek et al., 1990; Kilb et al., 2006; Roper et al., 1992; Rosen and Andrew, 1990; Saly and Andrew, 1993; Traynelis and Dingledine, 1989), particularly in regions such as the hippocampal CA1 where the ECS is smaller at baseline (McBain et al., 1990). Similarly, a recent study has found that genetic knockdown of the extracellular matrix glycosaminoglycan hyaluronan (HA) leads to a 40% ECS reduction within the CA1 stratum pyramidale and results in both ictal (seizure, or seizure-like) and interictal (inter-seizure) epileptiform activity. The epileptiform activity is subsequently abolished in hyperosmolar conditions known to cause cell shrinkage and increase the volume of the ECS (Arranz et al., 2014). Indeed, pre-seizure ECS constriction has been observed in multiple models of epilepsy (Binder et al., 2004b; Broberg et al., 2008; Traynelis and Dingledine, 1989). Tissue swelling may therefore represent both an important treatment target, and an important early warning sign, for seizures (Binder and Haut, 2013).

2.1. Water channels and brain volume

In general, brain water content is thought to be controlled by astrocytes due to their selective expression of the water channel aquaporin-4 (AQP4) (Nagelhus et al., 2004; Nielsen et al., 1997). AQP4 expression is particularly enriched at astrocytic endfeet adjoining cerebral vasculature, providing tight control of water fluxes both into and out of the brain (Amiry-Moghaddam et al., 2003a; Nagelhus et al., 2004; Nielsen et al., 1997). Consequently, the role of AQP4 in neurological disease reflects the role of water movements in said disease. For example, AQP4-dependent water movement through astrocytes is essential for clearance of vasogenic edema (plasma ultrafiltrate which leaks into and accumulates in the ECS). The same water permeability can exacerbate cellular/cytotoxic (intracellular) edema, making AQP4 a liability in cases of stroke (Katada et al., 2014), liver failure (Rama Rao et al., 2014) or other disorders which cause cell swelling in the brain (Papadopoulos and Verkman, 2007). Genetic deletion studies have provided evidence that AQP4 may be more than a simple, passive water channel, and is most likely not the sole mechanism for astrocyte water permeability. In one study, knockout of the anchoring protein α-syntrophin, which removes perivascular AQP4 (Amiry-Moghaddam et al., 2004), significantly inhibited swelling in severe (~33%) hypoosmolar conditions, but had no effect on swelling in mild (~17%) hypoosmolar conditions (Anderova et al., 2014). With a full knockout of $AQP4^{-/-}$, another study found nearly the opposite effect; little or no change in volume in 30% hypoosmolar solution, but significant reduction in volume at 20% (Thrane et al., 2011).

During synaptic transmission, AQP4 may be important for the activity-dependent fluxes of water which occur alongside potassium uptake and buffering in astrocytes. Increases in extracellular potassium, whether activity-induced or bath-applied, cause astrocyte swelling and a reduction in size of the ECS (Andrew and MacVicar, 1994; Dietzel et al., 1980; Holthoff and Witte, 1996; Risher et al., 2009; Walz and Hinks, 1985). Loss or mislocalization of AQP4 channels is reported to impair astrocyte $[K^+]_o$ clearance and buffering (Amiry-Moghaddam et al., 2003b; Binder et al., 2006; Eid et al., 2005; Haj-Yasein et al., 2015; Strohschein et al., 2011). Suppression of activity-dependent cell swelling has also been reported in $AQP4^{-/-}$ mice (Kitaura et al., 2009), but these data are inconsistent with more recent work in which AQP4 deletion led to an increase in activity-induced tissue swelling (Haj-Yasein et al., 2012). These disparate findings may result from regional astrocyte heterogeneity or methodological differences, but they also suggest that the