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# Pathological Changes of Astrocytes under Seizure

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## Abstract

Multiple lines of studies support the view that defective functions of astrocytes contribute to neuronal hyper-excitability in the epileptic brain. Autopsy and surgical resection specimens find that post-traumatic seizures and chronic temporal lobe epilepsy may originate from glial scars. Astrogliosis, a component of glial scar, which involves structural and metabolic changes in astrocytes, is often a prominent feature of temporal epilepsy and most animal models of recurrent seizures. Although glial scar formation has been recognized for over 120 years, fundamental aspects of the cellular mechanisms are poorly understood. We here provide an overview of the experimental findings about astrogliosis in seizures, which involves the changes in astrocytic structure and loss of domain. These structure changes are paralleled by functional changes, including expression levels of glutamate transporter and glutamine synthetase. Reactive astrocytes have also been shown to down-regulate the activities of $K^+$ channels, leading to impairment of clearance of $K^+$. The functional remodeling may contribute to increased neuronal excitability and generation of seizures.

## Keywords

Astrocyte, Astrogliosis, Seizure, Potassium, Glial scar
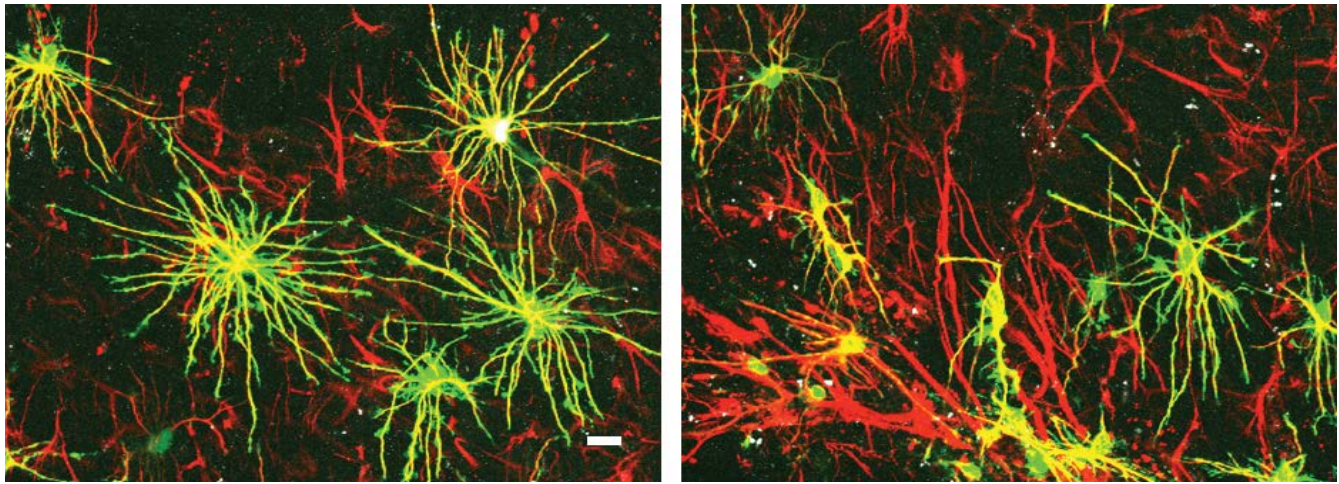
## Introduction

Epilepsy is a common chronic neurologic disorder affecting at least 50 million people [1,2], or more than 1% of the population worldwide [3-5]. Epileptic seizures are uncontrolled sudden attacks of a non-convulsive or convulsive nature associated with intensive neuronal firing. Spatially restricted foci in seizure brain can often be identified for epilepsies acquired after tumors, head trauma, or other severe focal brain, insults brain [6]. The cellular or molecular mechanisms underlying epileptic form activity have not been fully understood, but the contributions of astrocytic cells have been suggested by many studies.

Astrocytes are the most abundant glial cell type in the brain [7], which are characterized by leaflet-like processes and very irregularly shaped cell bodies, and cover almost all excitatory synapses in the brain [7,8]. Historically, glial cells were only thought to provide neurons with only metabolic and physical supports, to control the ionic homeostasis, and control the neuronal excitability through $K^+$ buffering, and serve as the primary energy source for neurons [9,10]. Current research has expanded their function to important homeostatic and neuronal modulatory functions [11]. Astrocytes are involved in regulating ion homeostasis, maintenance of the blood brain barrier (BBB) function, metabolism of amino acid neurotransmitter, as well as nutrient and energy support for neurons [12]. Our recent reports demonstrated that astrocytes could actively regulate these processes with intracellular $Ca^{2+}$ wave regulated signaling pathways [13,14]. The present review summarized the roles of reactive astrocytes in the development and progression of epileptic seizures, and discussed the relevance of calcium signaling in astrocytes to therapeutic management of the disease.

## Astrogliosis after Brain Injury

Almost all traumatic brain injury (TBI), including prolonged seizures, results in reactive gliosis (astrogliosis), which are characterized by severe biochemical and morphological changes of pre-existing astrocytes and also new astrocyte generation. These astrocytes constitute a dense scar tissue that has been suggested to separate the injured tissue from its surroundings and demarcate the lesion area. Experimental ablation of astrocytes after TBI results in larger lesions, worse demyelination, local tissue disruption, and exacerbated neuron death. Activated astrocytes is beneficial in that they produce a barrier against the spread of neurotoxicity and prevent excitatory amino acid induced cell death [15]. The glial scar consists predominately of microglia, reactive astrocytes, and extracellular matrix molecules, such as chondroitin sulfate proteoglycans. The reactive astrocytes provide metabolic and tropic support to prevent secondary degeneration. In addition, astrocytes provide tropic support at the injury site which promotes the survival of nearby neurons. Though astroglial scars are essential for wound repair, they also interfere with axonal regrowth [16]. Their effects of inhibiting axon regrowth have been studied and described in considerable mechanistic and descriptive detail. For instance, it was found that the astrocytes are oriented perpendicular to lesions during scar border formation, and they quantifiably reorient to become more or less parallel to the lesion as scar formation progresses. And it is found that the initial perpendicular orientation of the elongated astrocytes appear remarkably similar to that of palisading astrocytes perpendicular to cortical lesions after TBI and implicated in post TBI epileptic foci [17]. In addition, the mechanisms of glial scar inducing seizure are also possibly due to astrogliosis, with its ability of $K^+$ buffering and neurotransmitter clear up decreased.

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**Figure 1:** Loss of astrocytic domain organization after brain injury.

Left: astrocyte in normal conditions; Right: new astrocytes and normal astrocytes at the glial scar mixed together, demonstrating loss of the domain organization, modified from Oberheim et al [17]. Green, GFAP; red, DiD; scale bar = 20 μm.

## Cytokines Released by Reactive Astrocytes

Although glial scar formation has been recognized for over 120 years, fundamental aspects of the cellular mechanisms, molecular regulation, and adaptive function underlying astrogliosis remain poorly understood [16]. Lesion-derived diffusible inflammatory factors such as cytokines, growth factors might be involved, for signaling mechanisms that determine astrogliosis have for some time been associated with penetrating CNS lesions that disrupt the BBB, instead of CNS insults where BBB function is preserved; and astrogliosis varies according to the distance from lesions [16]. Dysfunction of the BBB is a hallmark of brain insults and usually surrounds the core lesion. Focal epilepsy typically arises either within or adjacent to a cortical lesion [18].

Astrocytes can produce many pro- and anti-inflammatory molecules and have dynamic functions. The production of TGF-β and TNF-α by astrocytes can lead to detrimental effects depending on the receptors activated and expression timing [19]. TGF-βs play a critical role in the intercellular communication, and are involved in embryogenesis, cell growth, would healing, morphogenesis, and apoptosis in a wide variety of cells [18]. TGF-β1 expression is up-regulated in the brains suffering from Alzheimer's disease, stroke, multiple sclerosis, tumor or traumas. TGF-βs have also been found to be elevated in the cerebro-spinal fluid (CSF) of patients with brain injury [20]. The preferentially uptake of serum albumin by glial cells within hours following brain injury in prior to the seizure development [21], raised the hypothesis that glial functions and dysfunctions play a critical role in the epileptic generation [18]. Aronica et al further reported that the up-regulated expression of TGF-β in astrocytes from the hippocampus of SE-experienced rats [22].

Multiple inflammatory factors induced by pathologically TBI induced changes have been described, for example, growth factors such as TNF-α, TGF-β can induce changes in neuronal calcium homeostasis. The release of TNF-α, TGF-β could be released by astrocytes in responses to excitotoxic injection. The epileptic brain can also be induced by astrocytic dys-regulation of the vascular system. The up-regulation or induction of IL-1β, complement components, and many other inflammatory factors within perivascular astrocytes, may have dramatic effects on the vascular system leading to disruption of the BBB [23]. Recent studies from several laboratories confirmed the role of vascular pathology in the epileptic development and demonstrated a critical role for astrocytes in epilepsy. Mechanical stimulation under pathological conditions could provide the injured CNS with impaired domain, mass effects, swelling, or tissue hypertrophy [24].

Reactive astrocytes are characterized by up-regulation of glial fibrillary acidic protein (GFAP) expression and significant hypertrophy of cell bodies and processes. Interestingly, the severity of astrocygliosis is often a predictor of post TBI seizure, and intra-operative recordings have found that post TBI seizures and temporal lobe epilepsy are often initiated in, or immediately adjacent to glial scar tissue (McKhann 2000). Our previous studies found that a marked increase in overlap of processes between adjacent astrocytes after brain injury (Figure 1). There are two distinct types of reactive astrocytes in animals with focal epilepsy: hypertropic astrocytes, which located just beyond the annular sector occupied by palisading astrocytes; and palisading astrocytes, which immediately surround the injury site, whose processes form a halo around the lesion with striking radial orientation. The hypertropic astrocytes plays an important role in pathogenesis of seizures by releasing the cytokines, and also exert a continued deleterious effect on tissue [25]. Palisading astrocytes exhibited a complete loss of individual domains and appeared to form a physical barrier separating the lesion from the surrounding cortical tissue. Astrocytes are possibly organized in non-overlapping domains, and the loss of domain due to astrocytic structure changes are paralleled by functional changes, such as expression levels of glutamine synthetase and glutamate transporter.

## Astrocytic Modulation of Glutamate

The astrocytic function of housekeeping is to maintain a low concentration of extracellular glutamate and prevent excitotoxicity. Astrocytic uptake of glutamate terminates the effects of glutamate as a neurotransmitter [26,27]. And it is commonly accepted that GLT-1 transporters (excitatory amino acid transporter-2/EAAT2) in astrocytes play a large role in glutamate uptake. High affinity glutamate transporters, GLAST1 and GLT1 subtype, are enriched in astrocytic processes, and play the predominant role for glutamate clearance in the brain. Glutamate transporting is an electrogenic and energy demanding process, with one glutamate being co-transported with three $Na^+$. And then glutamate is converted to glutamine via an ATP-consuming process, catalyzed by a glutamine synthetase, an astrocyte-specific enzyme, in the astrocytes. Glutamine is subsequently released to fuel the neurons and recycled into glutamate for glutamatergic neurotransmission. Glutamine synthetase (GS) plays a critical role in the glutamate metabolism [26], and glutamine synthetase has been shown to be up-regulated in reactive astrocytes. But it appears to be reduced in the epileptic hippocampus, indicating potential changes in the astrocytic transporters. Similiar change of glutamate transporters have similarly been shown to be reduced in the epileptic hippocampus [28], which might be due to $Na^+$, $K^+$-ATPase impairment affected by high extracellular $K^+$.
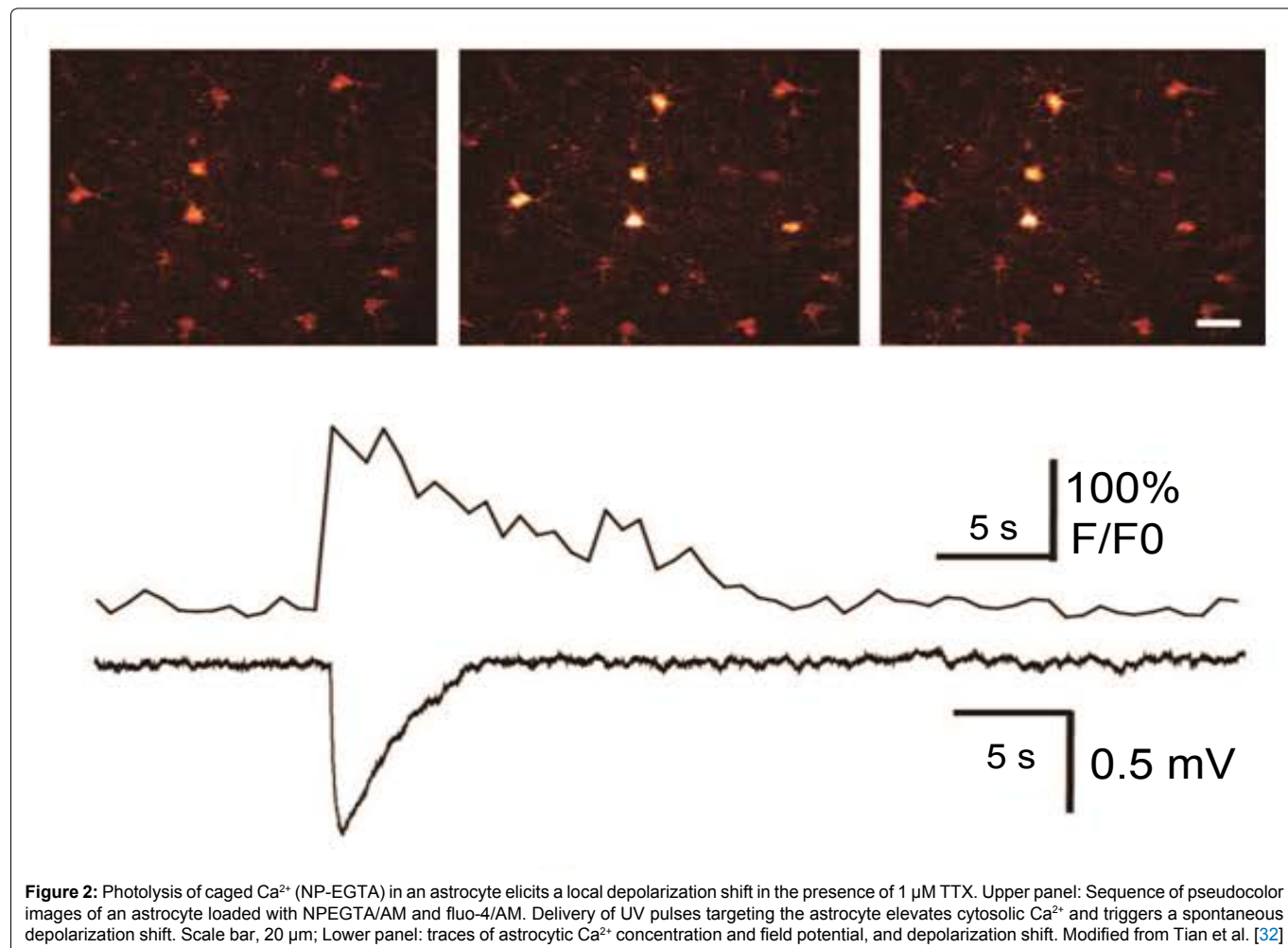
It is now reported that peri-synaptic astrocyte may detect spillout of glutamate and other substances from active synapses under seizures and respond structurally by modifying and extending their processes.
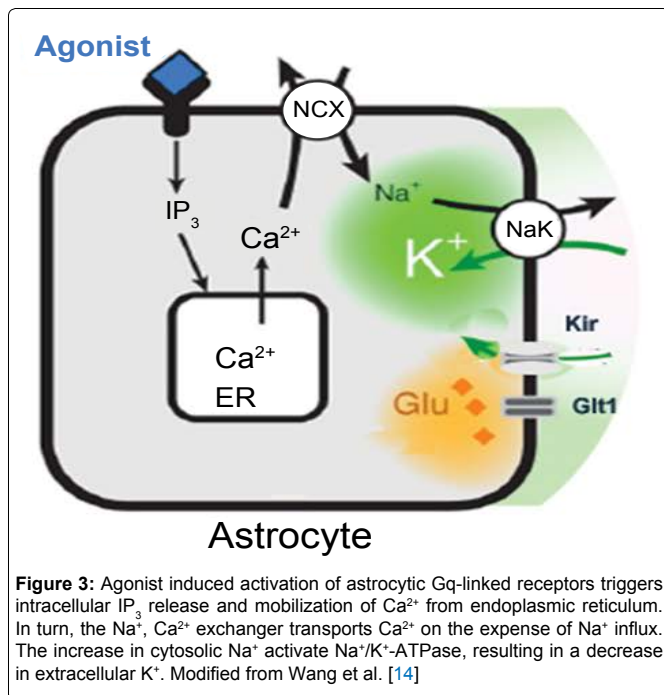
Astrocytes respond to synaptic neurotransmitters release with both $Ca^{2+}$ waves and glio transmitter release that can further enhancing seizures, with important implications in the epileptic brain [29]. In addition, astrocytes can also modulate synaptic function and modulate inter-synaptic crosstalk via regulation of extracellular glutamate diffusion. In addition, glutamate can interact with mGLuR to induce astroglial cell swelling by modulating intracellular $Ca^{2+}$, which can be detected simultaneously with changes in cell volume. Expressions of the EAAT2 transporters are significantly decreased in CA1 region in the sclerotic human hippocampus. In addition, sclerotic brain tissues removed during epilepsy surgery are characterized by down-regulation of glutamate synthetase in astrocytes [30]. The glutamate cycle is the major way to remove released glutamate from extracellular space. Following its synaptic release from the glutamatergic neuron terminals, glutamate is transported into astrocytes where it is converted into glutamine by glutamine synthase; glutamine is exported and taken up by neurons, where it is converted back to glutamate by mitochondrial glutaminase. Indeed, glutamate-glutamine cycling appears to be slowed in sclerotic hippocampus removed during epilepsy surgery [31]. With this process slowing down, intracellular glutamate might be increased and released into extracellular space, and astrocytic glutamate signaling might be enhanced. There is no question that glutamate can act as a key transmitter of bidirectional communication between astrocytes and neurons, and many studies have pointed out that astrocytes can release glutamate. Previous studies in our lab suggested the role of astrocytes in initiation, maintenance and spread of epileptiform activities by astrocytic glutamate release (Figure 2) [32]. Synchronized population spikes are key concomitants to seizure. Some studies have indicated multi-synaptic excitatory pathways can trigger synchronized burst activity in picrotoxin (GABA$_A$ receptor blocker)-induced seizure activity, while some other evidence pointed to the roles of both recurrent inhibition and gap-junction coupling. Studies in our lab suggested that an action-independent source of glutamate can trigger local depolarization events and synchronized bursting activity.

## Increase in $[K^+]_O$ can Induce Paroxysmal Oscillation

It is found that $K^+$ buffering is impaired in sclerotic tissue, by comparison of hippocampal slices obtained from patients without or with or mesial temporal sclerosis [33]. Impaired astrocytic $K^+$ buffering is expected to result in slower $K^+$ clearance, lower seizure threshold and thereby contributing to seizure generation. The concentration of extracellular $K^+$ is an important factor that regulates the neuronal excitability in the neural network [9,10]. Extracellular $K^+$ accumulation is considered to be a favorable condition for the seizure onset, and impaired $K^+$ uptake by astrocytes might be the initiation of epileptiform activity in the hippocampus. It is estimated that the passage of a single action potential can trigger 1 mM transient increase in extracellular $K^+$( $[K^+]_o$ ), above the ~3 mM resting level. Intensive neuronal stimulation causes nearly 5 mM an increase above the resting level. Peaks of 10-12 mM $K^+$ can be reached during hyper-synchronous neuronal activities that characterized epileptic disorders [29,34]. Increased $K^+$ due to intense neuronal firing discharges can depolarize neurons and facilitate the development of epileptiform discharges [35]. However, even though it is well established that the extracellular $[K^+]_o$ concentration increases during seizure, but whether astrocytic buffering imparing is the primary seizure-eliciting factor remains unknown. Astrocytes play an essential role in maintenance of extracellular $K^+$ at a level compatible with normal neuronal activity [11]. In vitro studies have shown that stimulation-induced $K^+$ increases are paralleled by $K^+$ accumulation in astrocytes, suggesting the roles of astrocytes in $K^+$ regulation [36]. The level of $K^+$ was determined by $K^+$ mediated currents, glial buffering and $K^+$ pump [14]. Our studies also suggested that agonist induced $Ca^{2+}$ wave can facilitate the extracellular $K^+$ uptake (Figure 3) [13,14,37], but when either $K^+$ pump or glial buffering failed to act normally, the $K^+$ increase leads to paroxysmal bursting. In addition, with $K^+$ buffering ability decreases, many other functions might also be affected, such as intracellular $Cl^-$ will also be increased. With intracellular $Cl^-$ increase, the inhibition pathway was impaired [38].



**Figure 2:** Photolysis of caged $Ca^{2+}$ (NP-EGTA) in an astrocyte elicits a local depolarization shift in the presence of 1 μM TTX. Upper panel: Sequence of pseudocolor images of an astrocyte loaded with NPEGTA/AM and fluo-4/AM. Delivery of UV pulses targeting the astrocyte elevates cytosolic $Ca^{2+}$ and triggers a spontaneous depolarization shift. Scale bar, 20 μm; Lower panel: traces of astrocytic $Ca^{2+}$ concentration and field potential, and depolarization shift. Modified from Tian et al. [32]

**Figure 3:** Agonist induced activation of astrocytic Gq-linked receptors triggers intracellular $IP_3$ release and mobilization of $Ca^{2+}$ from endoplasmic reticulum. In turn, the $Na^+$, $Ca^{2+}$ exchanger transports $Ca^{2+}$ on the expense of $Na^+$ influx. The increase in cytosolic $Na^+$ activate $Na^+/K^+$-ATPase, resulting in a decrease in extracellular $K^+$. Modified from Wang et al. [14].

## Conclusion

Epilepsy is a common chronic neurologic disorder affecting ~1% of the population with an estimated lifetime risk greater than 4%. In spite of optimal medical management, many patients with epilepsy remain medically refractory and suffer from debilitating seizures. Treatment options for these patients include new antiepileptic drugs, which target ion channels, such as $Na^+$, $Ca^{2+}$ channels or GABA receptors. These drugs are only effective in a small percentage of patients, not as effective as resective surgery which are effective in 60~80% of patients. So far there are few treatments targeting astrocytes, even though many studies pointed to astrocytic cells. Historically, astrocytes were thought to provide only physical and metabolic support for neurons, serving as the primary energy source for neurons and maintaining the water and ionic homeostasis and buffering $K^+$. In addition, it is now clear that astrocyte can release of gliotransmitters in response to synaptic neurotransmitters induced $Ca^{2+}$ waves and that in turn can further influence synaptic activity, with important implications in the epileptic brain [29]. Astrocytes play a critical role in glutamate uptake, mostly through the GlT-1 transporter, with assistance by additional uptake via the EAAT1 transporters. Glutamine synthetase plays a key role in the metabolism of uptaken glutamate. In addition, the major housekeeping functions of astrocytes include the maintenance of extracellular $K^+$ homeostasis [37]. Some investigators reported changes in the pathological changes of glial cells in epileptic scar tissue, and these astrocytes failed to take $K^+$ [39]. In conclusion, astrocytes are highly complex cells, and function to support the neuronal microenvironment and to modulate the excitability of neural networks under seizures [40]. Many properties of astrocytes also make them important targets for the developing field of treatment of epilepsy.

## Conflicts of Interest

The authors declare that there are no competing financial interests.

## Acknowledgements

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