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Blood–brain barrier dysfunction, status epilepticus, seizures, and epilepsy: A puzzle of a chicken and egg?

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Summary

Status epilepticus is often associated with endothelial dysfunction and increased vessels permeability. We discuss here the direct role of blood–brain barrier (BBB) dysfunction in epileptogenesis and brain damage. On the cellular level, astrocytes respond early to the efflux of serum proteins in the presence of dysfunctional BBB, with activation of the innate immune system and disturbed homeostasis of extracellular potassium and glutamate. In turn, there is enhanced excitability of neurons and altered network connectivity. Transforming growth factor beta (TGF-β) signaling appears to be a potential new target for the prevention of epileptogenesis and secondary damage following status epilepticus.

KEY WORDS: Astrocytes, Microglia, Serum albumin, Transforming growth factor beta.

Status epilepticus (SE) is often associated with endothelial dysfunction and increased vessels permeability. The direct role of blood–brain barrier (BBB) dysfunction in epileptogenesis and brain damage is discussed in subsequent paragraphs. On the cellular level, astrocytes are the early responders to the efflux of serum proteins in the presence of dysfunctional BBB. Astrocytic responses include the activation of the innate immune system and disturbed homeostasis of extracellular potassium and glutamate. These astrocytic changes, in turn, are associated with enhanced excitability of neurons and altered network connectivity. Transforming growth factor beta (TGF-β) signaling appears to be a critical pathway in the astrocytic response to serum albumin and thus may be a potential new target for the prevention of epileptogenesis and secondary damage following status epilepticus.

Prolonged seizure and SE are neurologic emergencies that may be followed by the development of unprovoked seizures as well as mental and neurologic deficits. Under physiologic conditions, seizures are associated with a robust vascular response (vasodilation) and increased regional cerebral blood flow. Although this neurovascular coupling may be considered as a physiologic homeostatic response to increased metabolic demand, recent animal and human data suggest that under pathologic conditions the physiologic coupling may fail, and neuronal depolarization may be associated with no or ''inverse coupling''—that is, vasoconstriction (Dreier, 2011). Pathologic vascular response may lead to reduced energy supply and worsening of the tissue metabolic state, thus promoting cellular damage and slowing energy-demanding homeostatic mechanisms such as active transporters required for neuronal repolarization. These changes will prolong neuronal depolarization and delay the termination of seizures. In addition, a metabolic compromise may also be associated with functional changes within vascular endothelial cells, leading to increased vascular permeability. Indeed, vascular dysfunction and increased permeability of the BBB have been documented following SE as well as under different common brain insults. The ''chicken and egg'' dilemma directly questions the role of BBB dysfunction in the pathophysiology of brain damage associated with SE. In this presentation I discuss the direct role of BBB dysfunction in SE, epileptogenesis, and brain damage.

The BBB is a functional and structural complex barrier characterizing the vasculature within the central nervous system and is crucial for the maintenance of a strict extracellular environment. Recent studies in pilocarpine-exposed rats (van Vliet et al., 2007) have described an increased number of spontaneous seizures in animals showing greater BBB dysfunction following SE, suggesting a potential direct role for BBB dysfunction in epileptogenesis. Indeed, our experiments in rodents demonstrated

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that dysfunction of the BBB underlies the initiation of transcriptional program within the neurovascular network (Cacheaux et al., 2009). This rapid transcriptional response is associated within a few hours with significant changes in the function of astrocytes (and probably also microglia), and includes up-regulation of cytokines and chemokines. Ex vivo experiments in the acute slice preparation show that the functional transformation of astrocytes is specifically associated with disturbed extracellular homeostasis leading to activity-dependent accumulation of potassium and glutamate in the extracellular space (David et al., 2009). These are followed by neuronal depolarization, slower spike repolarization, increased transmitter release, enhancement of glutamate content in the synaptic cleft, as well as activation of *N*-methyl-D-aspartate (NMDA) receptors and calcium influx. In turn, short-term synaptic facilitation and long-term synaptic modifications occur. The potential outcome of these changes was observed using in vivo recording showing that BBB opening was sufficient to result in the development of spontaneous unprovoked seizures 4–10 days after treatment in >80% of the animals. Sensorimotor neurologic dysfunction developed 3–5 weeks after focal BBB opening in the corresponding region of the neocortex, and was associated with loss of cortical volume [measured using in vivo magnetic resonance imaging (MRI) imaging], reduced dendritic branching, and neuronal loss with lasting astrogliosis (Tomkins et al., 2007).

The mechanisms underlying epileptogenesis and neuronal damage in the presence of BBB dysfunction are only partly understood. Specific attention has been given to serum albumin, which diffuses into the neuropil in SE-exposed animals and is transported into different populations of cells, probably via different mechanisms. Interestingly, although a selective uptake into astroglial cell populations has been found hours following the initiation of SE, 1–2 days later serum albumin [and immunoglobulin G, IgG] are found within principal hippocampal neurons. Direct exposure of brain tissue to albumin was associated with astroglial response via transforming growth factor beta (TGF-β) signaling and phosphorylation of the SMAD-2/5 pathway (Ivens et al., 2007; Cacheaux et al., 2009). Experimental data further suggest that blocking TGF-β signaling following experimental BBB opening decreases albumin-induced transcriptional response and prevents epileptogenesis. Finally, although limited, clinical data support a frequent BBB dysfunction in human patients with posttraumatic epilepsy (Tomkins et al., 2008) and its promoting effect in the development of seizures in patients with tumors (Marchi et al., 2007).

These studies point to the critical role of pathologic neurovascular interactions in astroglial dysfunction, immune response, neuronal hyperexcitability, and delayed network dysfunction and degeneration in the SE-exposed brain. Future studies are awaited to better diagnose vascular functions in clinical settings, and to explore their use as biomarkers for outcome and choice of treatment and their potential as targets for treatment (Friedman et al., 2009). The future development of new biomarkers and imaging approaches for the diagnosis of vascular and immune functions may be critical to allow specific treatments that will be tailored to the principal pathophysiologic mechanism(s) in an individual patient during and following status epilepticus.

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Disclosure

I have no conflicts of interest to declare. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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