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Review

Blood–brain barrier dysfunction in status epileptics: Mechanisms and role in epileptogenesis

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ABSTRACT

The blood–brain barrier (BBB), a unique anatomical and physiological interface between the central nervous system (CNS) and the peripheral circulation, is essential for the function of neural circuits. Interactions between the BBB, cerebral blood vessels, neurons, astrocytes, microglia, and pericytes form a dynamic functional unit known as the neurovascular unit (NVU). The NVU-BBB crosstalk plays a key role in the regulation of blood flow, response to injury, neuronal firing, and synaptic plasticity. Blood–brain barrier dysfunction (BBBD), a hallmark of brain injury, is a prominent finding in status epilepticus. Blood–brain barrier dysfunction is observed within the first hour of status epilepticus, and in epileptogenic brain regions, may last for months. Blood–brain barrier dysfunction was shown to have a role in astroglial dysfunction, neuroinflammation, increasing neural excitability, reduction of seizure threshold, excitatory synaptogenesis, impaired plasticity, and epileptogenesis. A key signaling pathway associated with BBBD-induced neurovascular dysfunction is the transforming growth factor beta (TGF-β) proinflammatory pathway, activated by the extravasation of serum albumin into the brain when BBB functions are compromised. Specific small molecules blocking TGF-β, and the nonspecific, Food and Drug Administration (FDA) approved blocker and angiotensin antagonist losartan, were shown to reduce BBBD and block epileptogenesis. With these encouraging preclinical data, we have developed imaging approach to quantitatively assess BBBD as a diagnostic, predictive, and pharmacodynamic biomarker after brain injury. Clinical trials in the foreseen future are expected to test the feasibility of BBB-targeted diagnostic coupled therapy in status epileptics and seizure disorders.

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1. Blood–brain barrier dysfunction in neuropathology

The neural environment is preserved within a narrow homeostatic range to maintain normal brain function. The blood–brain barrier (BBB), a unique anatomical and physiological interface between the central nervous system (CNS) and the peripheral circulation, was first described by Paul Ehrlich in the 19th century [1]. The signaling pathways and functional interactions between the BBB, cerebral vessels, neurons, astrocytes, microglia, and pericytes form a dynamic functional unit known as the neurovascular unit (NVU). The NVU-BBB crosstalk plays a key role in the regulation of blood flow, response to injury, neuronal firing, and synaptic plasticity required for brain function in health and disease [2]. Intact BBB is essential for maintaining a microenvironment that allows neuronal circuits to function properly. As detailed below, BBB dysfunction (BBBD) leads to the extravasation of plasma proteins and immune cells into the brain neuropil, changes in astroglial functions, ionic derangement, and potential entry of toxins, drugs, and pathogens into the CNS, which in turn, may lead to neuronal dysfunction, neuroinflammation, and neurodegeneration [3]. Blood–brain barrier dysfunction has been shown to have a pivotal role in the pathophysiology of diseases associated with neuronal hyperexcitability, such as acquired epilepsy [4], traumatic brain injury [5], stroke [6], and migraine headache [7].

2. Status epilepticus is associated with blood–brain barrier dysfunction

Status epilepticus (SE) is associated with high mortality, and survivors often suffer from neurological complications, including epilepsy

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and cognitive impairments. Extensive animal research has been conducted to study the consequences of SE [8]. In vivo, experimental models for SE induction include chemical agents, such as organophosphates (OP), pilocarpine, or kainic acid, as well as electrical stimulation of the amygdala or hippocampus [8–11]. Status epilepticus has been shown to cause excitotoxicity, brain edema, cell loss, reactive gliosis, and neural dysfunction, associated with cognitive deterioration and the development of epilepsy [12]. Postmortem histopathological analyses from children and adults died of SE revealed neuronal loss in the amygdala, hippocampus, thalamus, cerebellum, and middle cortical layers [13]. These findings are consistent with brain damage found in animal models of SE [14,15].

Notably, SE is associated with a rapid and a robust increase in BBB permeability. In animal models of SE, treatment with midazolam, an anticonvulsant benzodiazepine, within the first 30 min of SE, quickly terminated seizures and led to acquired epilepsy in approximately 50% of the rats [10]. In this model, quantifying BBB leakage reveals that extent and localization of BBBD at 48 h is a highly sensitive and specific predictor for the development of epilepsy 4–8 weeks later [15]. Postmortem histopathological analysis confirms the leakage of the serum proteins albumin and IgG, the presence of reactive astrocytes and microglia, cellular damage, and associated neuroinflammation within the permeable brain regions. Interestingly, the piriform cortex was found as the brain region, in which the extent of BBBD best predicts the development of epilepsy, while BBBD in other brain regions (thalamus, septum) was associated with severe brain injury but with no apparent convulsive or electrographic cortical seizures. These results are consistent with other animal models of SE showing BBBD and robust inflammatory response, such as pilocarpine-induced SE [9,16,17], kainic acid-induced SE [11,18], as well as electrical stimulation-induced SE [14,19,20].

The mechanisms underlying BBBD are not fully known. Several novel BBBD-driven animal models of epileptogenesis have demonstrated the close association between BBBD and neuronal hyperexcitability [21]. We found that exposing the rodent neocortex to epileptogenic substances, such 4-aminopyridine (4AP) and picrotoxin (PTX), leads to increased BBB permeability within minutes of seizure onset [22]. Accumulating evidence support the role of glutamatergic spillover in permeability changes. Status epilepticus is associated with elevated levels of glutamate in the extracellular environment [23–27]. In vitro studies in cultured endothelial cells confirmed the expression of ionotropic and metabotropic glutamate receptors in brain endothelial cells [28], and that glutamate enhances endothelial permeability through reduction in transcellular trafficking resistance [29] and alteration in tight junction phenotype [30]. Glutamate activation in cerebral endothelial cells has also been documented to induce increase in intracellular calcium and oxidative stress [31,32], both were associated with increased barrier permeability [33]. Studies in vivo confirm that glutamate, at pathologically relevant concentrations, induces increased intracellular calcium in cerebral vessels, as well as BBB permeability in a dose-dependent manner [22]. These effects were found to be mediated by N-methyl-D-aspartate (NMDA) receptors.

3. Status epilepticus-induced blood–brain barrier dysfunction: the role of pericytes

Pericytes are small contractile cells situated around capillaries and participate in the formation of the NVU. In addition to their function as regulators of blood flow, pericytes have been suggested to play an important role in BBB formation during embryogenesis and maintenance BBB integrity [34,35]. Pericytic injury has been reported to be associated with vascular-mediated neurodegeneration [36] and ischemic stroke [37]. In addition, pericytes were found to actively participate in neuroinflammatory response by secreting proinflammatory cytokines [38] and to promote infiltration of peripheral immune cells into the brain [39,40]. Proliferation and rearrangement of pericytes were shown after SE and during epileptogenesis [41,42]. Evidence for the active participation of pericytes in the "seizure network" has been demonstrated recently in experiments using whole cell patch recordings from pericytes in the slice culture preparation. Triggering acute seizures was associated with simultaneous, prolonged inward current in pericytes. Recurrent seizures were followed by pericytic injury, loss of contractility properties, and BBBD. Indeed, slice culture and in vivo experiments confirmed reduced vasodilatory response to recurrent seizures, in both capillaries and arterioles [43].

4. From blood–brain barrier dysfunction to network modifications and epilepsy

Blood–brain barrier dysfunction is common in epileptogenic injuries, including SE, traumatic, and ischemic brain injuries. The signaling cascade following BBBD, and its role in network modifications underlying neuronal hyperexcitability and epileptogenesis have been described by our group [44–51] and others [52]. In short, BBBD after injury is associated with the extravasation of serum albumin into the brain tissue. Serum albumin binds to transforming growth factor beta receptors (TGF-βRs) in astrocytes, leading to Smad2/3 phosphorylation [48]. The resulting transcriptional modification involves the following: (1) a robust neuroinflammatory response, with an early upregulation of IL-6 [50], IL-1beta [53], and likely other proinflammatory cytokines; (2) downregulation of inward-rectifying potassium (Kir 4.1) channels and excitatory amino acid transporters (EAATs), leading to dysregulation of the extracellular environment and activity-dependent accumulation of potassium and glutamate [47]; (3) upregulation of matrix metalloproteases and changes in the perineuronal microenvironment [54]; (4) excitatory synaptogenesis [51]; and (5) pathological synaptic plasticity and rewiring of neuronal network [55]. These cellular and molecular events are likely to underlie the observed increased excitability and reduced seizure threshold [44–46].

5. Summary and future perspectives: from bench to bed and the path to translation

Studies in experimental models of brain injuries from numerous groups point to the central role of BBBD in neuropathology, including epilepsy. Our group has demonstrated that intravenous or intraventricular administration of specific TGF-β signaling pathway blockers prevents albumin-induced astrocytic activation, synaptogenesis, and pathological plasticity in vitro and in vivo [51,55,56]. We further showed the protective effect of losartan, a Food and Drug Administration (FDA) approved angiotensin II type 1 receptor blocker (ARB) known to block TGF-β signaling in peripheral tissue. When given to rats following status epilepticus or chemical opening of the BBB, losartan prevented albumin-mediated brain TGF-β signaling and reactive astrogliosis, reduced BBBD, and blocked epileptogenesis in the majority of treated animals [15,56]. These results are in agreement with studies from other groups showing the antiepileptogenic and neuroprotective role of losartan in different experimental models of epileptogenesis and brain injury [57,58]. Since epilepsy develops only in a relatively small fraction of patients following brain injury, a key prerequisite for clinical trials would be the development of a predicting biomarker to identify patients at high risk to develop epilepsy [59]. First promising steps into this direction are underway and should be tested in preclinical [15] and clinical studies [60,61]. This should allow an accurate and clinically reliable quantitative measures of BBBD as a diagnostic, predictive, and pharmacodynamic biomarker.

Declaration of competing interest

None.

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