Seminars in Cell & Developmental Biology 38 (2015) 26–34

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Blood–brain barrier dysfunction, seizures and epilepsy

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ARTICLE INFO

Article history:
Available online 6 November 2014

Keywords:
Blood–brain barrier
Temporal lobe epilepsy
Traumatic brain injury
Epileptogenesis
Albumin

ABSTRACT

The blood–brain barrier (BBB) is a dynamic and complex system which separates the brain from the blood. It helps to maintain the homeostasis of the brain, which is essential for normal neuronal functioning. BBB function is impaired in several neurological diseases, including epilepsy in which it may lead to abnormal and excessive neuronal firing. In this review we will discuss how BBB dysfunction can affect neuronal function and how this can lead to seizures and epilepsy. We will also summarize new therapies that aim to preserve or restore BBB function in order to prevent or reduce epileptogenesis.

Contents

1. Introduction

The blood–brain barrier (BBB) comprises of endothelial cells, which are connected via tight junctions [1]. Together with astrocytes, pericytes and neurons that are in close proximity of the endothelial cells [2] a neurovascular unit is formed that regulates the microenvironment in the brain. This is essential for proper functioning of neurons [1]. In various neurological disorders, including epilepsy, the BBB is disrupted. BBB dysfunction can have important consequences for neuronal excitability and can therefore be involved in the generation of seizures and epilepsy. There is ample evidence from experimental animal studies that BBB dysfunction can be caused by seizure activity (reviewed in [3–7]). However, research in the last decade shows that BBB disruption can also lead to epilepsy or aggravate the epileptic condition [8–16]. Since BBB dysfunction can also occur in brain diseases without the comorbidity of seizures or epilepsy it is not clear how BBB disruption can cause epilepsy by itself. In the following paragraphs we will focus on the question how and when BBB dysfunction can play a role in eliciting epileptic seizures (ictogenesis) and/or (progression of) epilepsy (epileptogenesis). Furthermore, we will discuss potential new BBB-targeting strategies with the aim to prevent or reduce epileptogenesis.

Abbreviations: BBB, blood–brain barrier; ICAM-1, intercellular adhesion molecule 1; IL1-β, interleukin 1β; miRNA, microRNA; mTOR, mammalian target of rapamycin; MTS, mesial temporal sclerosis; SE, status epilepticus; TGF-β, transforming growth factor β; TLE, temporal lobe epilepsy; VCAM-1, vascular adhesion molecule 1.

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http://dx.doi.org/10.1016/j.semcdb.2014.10.003
1084-9521/

2. Blood brain barrier dysfunction as a result of seizure activity

After the first experiments in 1885 by Ehrlich, who demonstrated that brain blood vessels are not permeable to dyes that are injected into the bloodstream [17], many other researchers used

this approach to measure BBB permeability. Depending on the dyes or markers used, the permeability of the BBB can be measured using electron microscopy, light microscopy or in vivo imaging (e.g. Optical or Magnetic Resonance Imaging). It has been known since the 1960s that seizures affect the BBB [18]. BBB disruption, as detected using the BBB tracers Evans Blue, Horse Radish Peroxidase or Fluorescein occurs within 5–30 min after acute seizures that are induced using pentylene tetrazole, bicuculline, pyridoxine or hyperthermia in several (limbic) brain regions of animals [19–22]. These studies all suggest that seizure activity can lead to BBB opening, which may be caused by acute hypertension [23–25]. However, it cannot be excluded that the chemoconvulsant agents that are used to induce seizures also affect BBB permeability. BBB disruption is also evident in humans after traumatic brain injury, status epilepticus (SE, see also Fig. 1) [8] and in temporal lobe epilepsy (TLE) animal models, such as the kainic acid-, pilocarpine- or electrical stimulation-induced post-SE model. Widespread BBB leakage occurs within minutes after SE in animals and lasts for several hours–days [8,26–36]. This confirms the findings in the acute seizure models in which chemoconvulsants are used. Although kainic acid and pilocarpine are chemoconvulsants that can also directly or indirectly affect the BBB, electrical stimulation of the brain leads to similar findings [8]. This suggests that BBB disruption can occur as a consequence of (prolonged) seizure activity. In the TLE animal models BBB leakage is observed in various brain regions including the hippocampus, but also in other limbic and extralimbic brain regions, such as the entorhinal cortex, piriform cortex, thalamus, amygdala, septum, endopiriform nucleus and substantia nigra. Interestingly, an increased metabolic activation is observed particularly in these brain regions during seizures [37–40]. Intense seizures can be followed by a spreading depression, a large change of the slow electrical potential and silencing of brain electrical activity [41]. Blood vessels in the brain can respond to this activity with tone alterations, causing either transient hyperperfusion (physiological hemodynamic response) in healthy tissue or severe hypoperfusion (inverse hemodynamic response) in tissue at risk for progressive damage [41,42]. The latter will lead to less energy supply which promotes cellular damage and BBB disruption. In addition, increased systemic blood pressure, decreased blood pH and hypoxia in the brain may further contribute to BBB disruption [43].

The question whether a single seizure can open the BBB is not clearly answered in studies in which the post-SE models were used, since a SE is characterized by continuous seizure activity that usually lasts for several hours. However, a few attempts have been made to investigate the role of a single seizure on BBB permeability. Since spontaneous seizures occur after a latent period of several days–weeks in post-SE models, the effects of seizure activity can be studied on BBB permeability during the chronic epileptic phase, e.g. a few months after SE. This minimizes the acute effects of the SE on the BBB. Initially, major BBB leakage could be detected shortly after an initial insult using Magnetic Resonance Imaging or autoradiography [44,45], but these studies failed to detect the smaller BBB leakage during the chronic epileptic phase. However, by using the BBB tracer Fluorescein in combination with high resolution confocal microscopy Van Vliet et al. were able to show that BBB leakage occurs also during the chronic epileptic phase in rats as a result of a spontaneous seizure [8]. Interestingly, during this chronic phase the BBB tracers Fluorescein and Evans Blue are hardly detected in the extracellular space but are taken up by brain cells, which probably explains why previous studies failed to detect this subtle leakage. Moreover, the spontaneous seizure frequency is related with BBB leakage in the piriform cortical area (a brain region that is most affected after SE) of these rats. Furthermore, BBB leakage is observed for at least 1 h after the occurrence of a spontaneous seizure. These data suggest that a spontaneous seizure is associated with focal BBB leakage which probably may help to sustain the epileptic condition. This is confirmed by a recent study, in which the effects of a single bicuculline induced seizure are studied in the in vitro guinea pig brain model [46]. In this model, the BBB is disrupted within 5 min after an induced seizure and FITC-albumin extravasation is still observed 60 min later. This confirms the in vivo findings and suggests a long-lasting increase in BBB permeability after a single seizure.

Although it seems clear that acute seizures or a SE can induce BBB damage, it is not easy to determine whether disruption of the BBB during the chronic epileptic phase is just a consequence of seizure activity or that it can also contribute to the occurrence of seizures.

3. Blood brain barrier dysfunction in other epilepsy syndromes

Most of the BBB-epilepsy research mentioned above focuses on animal models of TLE after SE or epileptogenesis that occurs after traumatic brain injury. In these models an initial insult sets in motion the process of epileptogenesis. But what about the role of the BBB in other syndromes? The fact that increased albumin staining is also observed in focal lesions associated with drug resistant epilepsy (Fig. 1) such as in focal cortical dysplasia, tuberous sclerosis complex, gangliogliomas [47–49] and vascular malformations [50], suggests that disruption of the BBB could also play a role in these disorders. Whether a dysfunctional BBB plays a causal role may be investigated in more detail in animal models of these disorders (e.g. in conditional knockout mice for TSC1 [51]). Furthermore, BBB leakage is observed after perinatal asphyxia and is associated with the presence of seizures [52].

4. Are seizure activity and epilepsy caused by blood–brain barrier dysfunction?

In order to study whether BBB disruption can cause epilepsy, several research groups investigated changes of BBB permeability during epileptogenesis. This can be achieved by post-mortem microscopic analysis of BBB tracers that are applied just before animals are killed. In a recent study, is it shown BBB permeability can also be assessed in animals using in vivo magnetic resonance imaging in combination with infusion of a paramagnetic BBB tracer [32]. Several studies show that BBB permeability is most evident during the acute phase (shortly after SE), as described in the previous paragraph, but also extends into the latent phase in experimental models [8,32,34–36]. It is interesting to note that profound BBB leakage is detected during the acute and latent phases, when spontaneous seizures are still absent. This observation indicates that BBB disruption does not induce seizures immediately but is more likely to play a role in epileptogenesis. Similarly, while extensive BBB leakage is observed directly after traumatic brain injury in humans, seizure activity develops only at later time points [14–16,53].

Manipulation of the BBB in normal brain. In order to further investigate the role of BBB disruption in epilepsy, the BBB can be artificially opened by cortical application of bile salts in rats or by the administration of hypertonic mannitol via the carotid artery or the tail vein. The application of bile salts on the cortex of normal rats does not immediately induce seizures, since paroxysmal events are not observed before several days after application [9–11]. In another study, BBB opening by hyperosmolar mannitol that is injected via the tail vein of naïve rats does also not directly lead to seizures, although successful BBB opening has been confirmed by fluorescein extravasation in the brain [8,54]. Furthermore, intracarotid mannitol in normal rats opens the BBB, but does not change extracellular potassium or a CO_2-dependent intracortical direct