Chapter 2
Mechanisms of Cerebral Edema Leading to Early Seizures After Traumatic Brain Injury

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Abstract Epidemiological data support a link between traumatic brain injury (TBI) and seizures. TBI accounts for approximately 16 % of acute symptomatic seizures which usually occur in the first week after trauma. Children are at higher risk for posttraumatic seizures than adults and experience greater morbidity and mortality from cerebral edema (CE). CE is responsible for half of the mortality associated with TBI. A recent book chapter summarizes the most important features of posttraumatic seizure. In this chapter we will summarize features relevant to the link between cerebral edema, cerebrovascular events and seizures after TBI. In addition, we will discuss the potential autoimmune implications of TBI.

2.1 Introduction

Epidemiological data support a link between traumatic brain injury (TBI) and seizures. TBI accounts for approximately 16 % of acute symptomatic seizures which usually occur in the first week after trauma [1]. Children are at higher risk for posttraumatic seizures than adults and experience greater morbidity and mortality from cerebral edema (CE) [2]. CE is responsible for half of the mortality associated with TBI [3]. A recent book chapter summarizes the most important features of posttraumatic seizures [4]. In this chapter we will summarize features relevant to the link between cerebral edema, cerebrovascular events and seizures after TBI. In addition, we will discuss the potential autoimmune implications of TBI.

The mechanisms of early posttraumatic seizures and epilepsy following TBI are poorly understood. It is known that TBI causes both primary and secondary injury

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to the brain. Furthermore, the epileptogenic process may start with the initial insult to the brain which involves ionic, molecular, and cellular alterations resulting in cerebral edema and blood–brain barrier breakdown that may, or may not, lead to early seizures, late seizures, and/or epilepsy months to years following the initial trauma.

2.2 Posttraumatic Seizures

To study how TBI leads to changes in neuronal excitability, in human studies, one needs to focus on the fact that posttraumatic seizures refer only to seizures that occur *after* TBI and are *caused* by TBI. Exacerbation of preexisting seizures is not a good clinical example of post-TBI seizures. Another important preamble to this chapter is the acknowledgement that the temporal relationship between the traumatic event and seizures is a key factor in the underlying mechanisms of ictogenesis. Early posttraumatic seizures (hours after TBI; 2–5 % of all cases in mild TBI (mTBI); 10–15 % in severe TBI [2, 4, 5]) are likely different in mechanism from late seizures and are defined as occurring within 1 week of trauma.

Late seizures are most common after penetrating war-related events (53 % in Vietnam vets with penetrating TBI [5]). Additionally, 82 % of individuals who experience a late posttraumatic seizure will have another seizure within a year. This would suggest that patients be treated aggressively with anticonvulsant medication after a first unprovoked late seizure [6]. However, factors unrelated to TBI are at play in this population; these include infection, presence of foreign material in brain parenchyma, uncontrolled bleeding, etc. Recurrent seizures are chronic events that occur many months or years after TBI; whether these events are due to or consequence of late or early seizures remains unclear [7]. Use of acute prophylaxis to prevent conversion of early seizures into chronic epilepsy was suggested but the results were not conclusive [8].

Guidelines in the management of closed severe head injury recommend 1 week of anticonvulsants to prevent early seizures, though there is no effect on the risk of late seizures [9]. The prophylactic use of antiepileptic drugs should be short-lasting and therefore limited to the prevention of immediate and early seizures [10]. However, the routine use of antiepileptic drugs to prevent late posttraumatic seizures following severe TBI is not recommended.

2.3 The Blood–Brain Barrier

Prior to a discussion of edema etiology and its related pathologies, one must understand the homeostatic nature of cerebral ion gradients and how the blood–brain barrier (BBB) maintains optimal conditions in the brain. The BBB lines the cerebral microvasculature and is composed of, among other cellular

components, differentiated endothelial cells and the tight junctions (TJs) that link them together [11]. Endothelial cells of the BBB are differentiated in that they display less pinocytic activity, lack fenestrations, and have an increased number of mitochondria compared to endothelial cells in the peripheral vasculature. Exposure to luminal flow is a key factor in endothelial cell differentiation [12]. This functional differentiation is most likely due to the tight regulation of transcellular tansport into the brain. While there are a number of molecules that can freely cross the BBB (e.g., ethanol), most substances, particularly those that are large and/or hydrophilic, must cross the BBB via primary or secondary active transport (transport requiring ATP) or by virtue of existing concentration gradients. Energy-dependent transport across the BBB provides a mechanism by which movement of substances into the brain can be regulated based on the requirements of the cerebral environment. For instance, glucose transporters are upregulated on the luminal side of the membrane when cerebral nutrient supply becomes low [13].

Of particular importance to the maintenance of ion homeostasis and integral to any discussion of the blood–brain barrier are tight junctions. These structures provide a means by which endothelial cells can be physically linked together creating a continuous impermeable barrier and forcing the movement of ions and macromolecules to occur across the endothelial membrane or, in instances of TBI, across a disrupted BBB. TJs are comprised of a number of proteins including the integral membrane proteins occludin and claudins −3, −5, and −12. These proteins serve to form the characteristic paracellular seal of the BBB. In the cytoplasmic compartment, occludin and claudins are linked to the zonula occludens (ZO) family of adaptor proteins. ZO−1, −2, and −3 bind to claudins and ZO-1 binds to occludin. Adaptor proteins are bound to secondary adaptor proteins that anchor the junctional complex to the cytoskeleton. In addition to TJs, a secondary barrier, the adherens junction, is located below the TJ in the paracellular space. Adherens junctions serve to further limit vascular permeability [14]. There are a number of detailed reviews regarding the cellular and molecular biology of tight junctions and related BBB junctional complexes [15, 16].

2.4 Ion and Water Homeostasis

The BBB maintains ion gradients that are specific to the cerebral environment. Of particular importance to the discussion that follows are those that, when increased due to disruption of the BBB, lead to neuronal excitability. BBB disruption and the accompanying neuronal hyperexcitability promote seizures [17]. Further, directly increasing potassium levels in the brain has also been shown to cause seizures [18]. A summary of the concentration gradients that exist on either side of the BBB and their effect on neuronal excitability are shown in Fig. 2.1b. What follows is a brief discussion of the regulation of ions and molecules relevant to TBI and seizure in the context of brain edema.

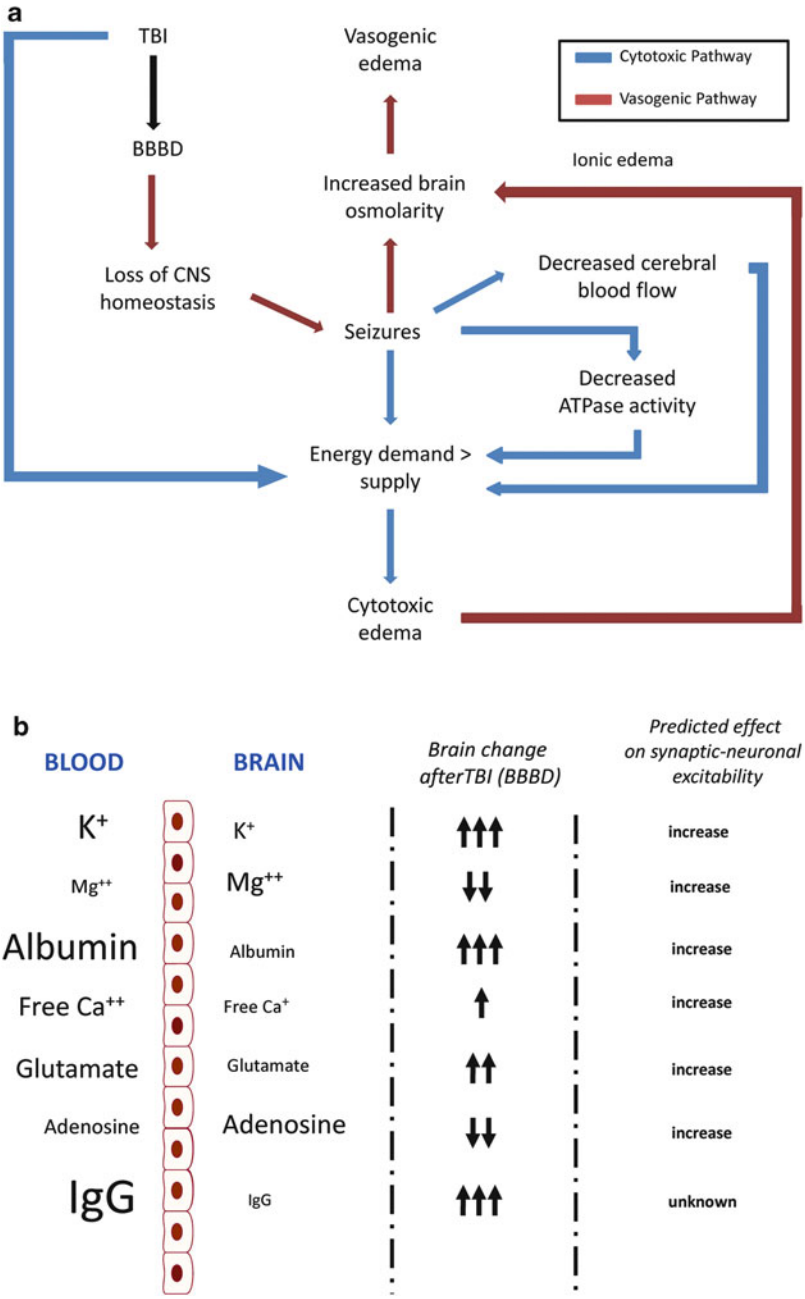


Fig. 2.1 (**a**) Mechanisms of homeostatic failure in the CNS. See text for details. (**b**) Quantitative gradients across the BBB and their predicted effect on neuronal excitability after TBI. The font sizes on the left and rights side of the idealized BBB are roughly proportional to their trans-BBB concentrations under homeostatic conditions. The brain concentration changes indicated by arrows are a semiquantitative means of showing what is expected after TBI induced BBB disruption

Potassium (K^+) regulation is key to the proper function of all excitable cells, including neurons [19]. K^+ in the brain extracellular space (ECS) is maintained at approximately 3 mM irrespective of serum potassium levels, though serum potassium is typically around 5 mM. Intracellular K^+ levels are kept high compared to the extracellular compartment (approximately 6 mM). There are therefore two distinct K^+ gradients: the gradient across cell membranes and the gradient across the BBB. This dramatic difference in concentration allows for the rapid repolarization required of CNS neurons after depolarization. However, neurons are unable to bring about such rapid changes in K^+ concentration alone. K^+ homeostasis is achieved via a glial buffering system in addition to the energy-dependent neuronal mechanism [20].

Neurons contribute to K^+ homeostasis through the Na^+/K^+ ATPase antiporter and sodium-potassium-chloride ($Na^+/K^+/Cl^-$) transporters. The Na^+/K^+ ATPase shuttles three Na^+ from the intracellular compartment and imports two K^+ into the cell per cycle of the pump. The $Na^+/K^+/Cl^-$ transporter moves ions in a 1:1:2 ratio, respectively, and will move ions in or out of the cell in order to maintain electroneutrality [21]. Glia, and in particular astroglia, play the largest role in K^+ buffering by two mechanisms: K^+ uptake and spatial buffering. In the K^+ uptake mechanism, astroglia remove K^+ in the ECS through a glial-specific Na^+/K^+ ATPase better suited for K^+ buffering than the neuronal isotype [22, 23]. Astrocytes also possess a $Na^+/K^+/Cl^-$ cotransporter (NKCC1) that has recently been implicated in potassium buffering [24]. Using these channels, astrocytes are able to temporarily sequester excess extracellular K^+ and release it back into the ECS when K^+ levels drop.

The second mechanism, spatial buffering, is a means by which astrocytes can remove K^+ from areas of high concentration and release it in areas of comparably lower concentration. This is achieved by a syncytium of astroglia connected by gap junctions that directly link neighboring cells [25]. In areas of high K^+ concentration, K^+ enters the cell primarily through potassium inward rectifier (Kir) channels, specifically Kir 4.1 [26]. Kir 4.1 channels localize at astrocyte foot processes [27]. These channels move K^+ into astrocytes and are unique in having a higher conductance at negative membrane potentials [28]. K^+ entry triggers a depolarization that travels through the astroglial network resulting in net outward movement of K^+. In this way, astrocytes are able to spread K^+ across a large area while causing only a transient increase in local intracellular K^+ concentrations [20].

The movement of water across the BBB and within the brain parenchyma follows osmotic gradients. In the brain, water moves through aquaporin channels, specifically aquaporin 1 and aquaporin 4 (AQP4). For the purposes of this discussion we will focus on the role of AQP4 as it is the primary water channel expressed on astrocytes and co-localizes with Kir 4.1 channels [29].

Fig. 2.1 (continued) (BBBD). Additionally, the predicted effect of altered BBB permeability on neuronal excitability is shown

Astrocytes express high levels of AQP4 on end-feet processes surrounding barrier capillaries; their proximity suggests a role in the regulation of water movement into and out of the brain parenchyma [29]. However, AQP4 can be found on end processes of astrocytes at synapses, suggesting an additional role in neuronal water uptake. It is interesting to note that immunocytochemical experiments do not detect the presence of the same aquaporin on neurons, indicating that astrocytes may be responsible for water homeostasis in the brain. AQP4 co-localization with Kir 4.1 channels suggests the coupling of K^+ and water movement within the brain as well as across the BBB [30]. The juxtaposition of these channels has led to the hypothesis that the astroglial syncytium may, in addition to the spatial buffering of potassium, redistribute water throughout the cortex and, in particular, perivascular areas thought to be sinks for excess water and K^+ [31]. Experiments have shown that an increase in extracellular K^+ leads to a decrease in ECS suggesting a link between K^+ and water movement [32]. Additionally, it has been demonstrated that Kir 4.1 channels and AQP4 channels may be associated, extracellularly, by the dystrophin-glycoprotein complex [33, 34].

Glutamate is an excitatory neurotransmitter whose concentration is tightly controlled across the BBB and in the ECS of the brain [35]. Concentrations of glutamate are considerably higher in blood than in the brain. Extracellular cerebral glutamate levels are maintained at approximately 1 μM while plasma glutamate levels are approximately 50 μM [36]. Similar to K^+, extracellular glutamate concentrations are regulated by astrocytes. Released at the synaptic cleft, excess glutamate is taken up by astrocytic processes that surround the synaptic cleft and are enriched with high affinity glutamate transporter 1 (GLT1) and glutamate aspartate transporter 1 (GLAST) receptors [37, 38]. Both transporters require the co-transport of Na^+ with H^+ and the movement of one K^+ and one bicarbonate (HCO_3^-) or OH^- out of the cell. Once in the cytoplasmic compartment of astroglia, glutamine synthase catalyzes the condensation of glutamate with ammonia to form glutamine. Glutamine is then released by the astrocyte and taken up by neurons that convert it back to glutamate.

2.5 Cerebral Edema

In general, CE is defined as an increase in total cerebral water volume leading to an increase in brain tissue volume and intracranial pressure (ICP) [39]. However, advances in basic and clinical science have shown this seemingly straightforward pathology to be a multifaceted process involving dramatic changes to intra/extracellular ion and water balance as well as changes in vascular permeability. Two broad categories of edema have been characterized and termed “cytotoxic” and “vasogenic” to refer to cellular swelling and increased vascular permeability, respectively. It must be noted that these two classifications of edema refer to events that rarely appear independently and are only useful to describe varying stages of a complex process. Additionally, there are a number of subclasses of cytotoxic and

vasogenic edemas that appear as either part of the edema process or occur under specific pathological circumstances. In clinical situations, patients will present with varying degrees of the different types of edema depending on the time course and severity of the injury [40].

2.6 Vasogenic Edema

As mentioned previously, the BBB is essential to maintain appropriate ion, protein, and water levels in the brain. After TBI the integrity of the BBB is compromised due to mechanical disruption of the endothelial cells and their associated TJs. It has been widely stated that BBB disruption alone will lead to an increase in water entry into the brain [41, 42]. However, the total osmolarity of blood and cerebrospinal fluid is equal (289 mOsm/L) [43] which could not produce the dramatic movement of water into the brain that is characteristic of vasogenic edema. There are two plausible mechanisms by which water moves into the brain parenchyma after BBB disruption. (1) K^+ moves down its concentration gradient from blood into the brain resulting in a K^+ concentration that is sufficient to depolarize neurons, trigger action potentials, and drive repolarization further elevating cerebral K^+ levels. This high K^+ may lead to disruption of the osmotic homeostasis between brain and blood causing water to move into the brain. (2) Cellular damage from traumatic insult results in intracellular protein release into the brain parenchyma. As extracellular protein levels are normally kept low in the brain, the addition of such a large amount of protein would perturb the osmotic balance between the brain and blood resulting in water influx into the brain.

Mechanical injury to the BBB is not the only cause of increased vascular permeability leading to vasogenic edema. A number of molecules released after TBI have been found to play an active role in either BBB disruption and/or increases in vascular permeability. Matrix metalloproteinases (MMP) are a family of endopeptidases that have been shown to degrade the TJs of the BBB after TBI. Specifically, MMP-2 and −9 have been associated with the degradation of Z0-1, claudin-5, and occludin [44–46]. MMP-2, -3, and −9 expression is increased after TBI. Increased MMP-9 activity, in particular, has been observed in areas of BBB disruption and edema. MMP-9 knockout mice have supported this hypothesis, showing a decrease in BBB breakdown, edema, and inflammation [47].

Two members of the kinin family of proteins, bradykinin and tachykinin have been linked to increased BBB disruption after TBI [48, 49]. Bradykinin acts through two G-protein-coupled receptors, B_1 and B_2, linked to phospholipase C. After TBI, both receptors are highly upregulated for approximately 24 h, but it appears that binding of bradykinin to the B_2 receptor most dramatically affects edema. B_2 receptor knockout mice show less edema after TBI [50]. Further, administration of B_2 receptor antagonists to mice after TBI has been shown to reduce ICP [51]. It should be noted, however, that the same result was not observed in human clinical trials [52].

Tachykinins are neuropeptides that have been linked to neurogenic inflammation [49]. A specific tachykinin, substance P, is a mediator of vascular permeability and has been linked to increased BBB permeability after TBI [53]. In the brain, substance P binds to a G-protein-coupled receptor, neurokinin-1, that acts through phospholipase C. Human studies have shown an increase in immunoreactivity to substance P after TBI and elevated immunoreactivity to substance P in cortical microvasculature [54]. Substance P is co-released from neurons with calcitonin-gene-related peptide (CGRP), a vasodilator known to enhance edema in the presence of molecules similar to substance P [55]. While the link between substance P and vasogenic edema has not been directly established, evidence does suggest a potential role for substance P in the process.

Irrespective of the mediators or mechanism, the result of increased vascular permeability associated with BBB disruption is the paracellular leakage of protein- and ion-rich fluid into the brain. This can lead to a number of complications. (1) The increase in ICP from fluid accumulation. Eventually ICP will cause the ICP to become greater than that of vascular pressure causing blood vessels to collapse and nutrient flow to stop [56]. (2) Excess extracellular ions and neurotransmitter will disrupt the delicate neuronal and glial homeostatic mechanisms which may result in seizure. (3) Immunoglobulins, immune cells, and inflammatory mediators normally kept out of the immunologically privileged brain now have access to nervous tissue [57]. Conversely, proteins normally sequestered in the brain will then have access to peripheral circulation and tissues [58]. (4) The BBB disruption following TBI may prohibit adequate treatment of elevated ICPs with osmotic agents (e.g., mannitol or hypertonic saline) as the gradient which would normally drive water out of the brain might be impaired. There are some recent preclinical studies indicating that modulation of the BBB using small inhibitory RNA directed against claudin-5 may markedly improve the outcome of patients with cerebral edema [59].

2.7 Cytotoxic Edema

Ischemic, hypoxic, and impact injuries that coincide with TBI have been shown to induce the initial signs (cellular swelling) of cytotoxic edema in as little as 30 min [60]. Cytotoxic edema is characterized by changes in osmotic balance between the intracellular compartment and the ECS. This osmotic perturbation leads to an increase in cell volume and a 16 % [61] decrease in the volume of the ECS. However, this process does not directly lead to swelling of the brain, rather a net movement of water from the ECS to the intracellular compartment. Swelling of the brain may occur as a consequence of the ion gradient setup between the ECS and cerebral microvasculature in the absence of BBB disruption (Fig. 2.2). This gradient, caused by depletion of Na^+, water, and Cl^-, promotes the movement of ions and water across the BBB into the ECS leading to an increase in ICP [62]. This secondary movement of ions has been termed “ionic edema.”

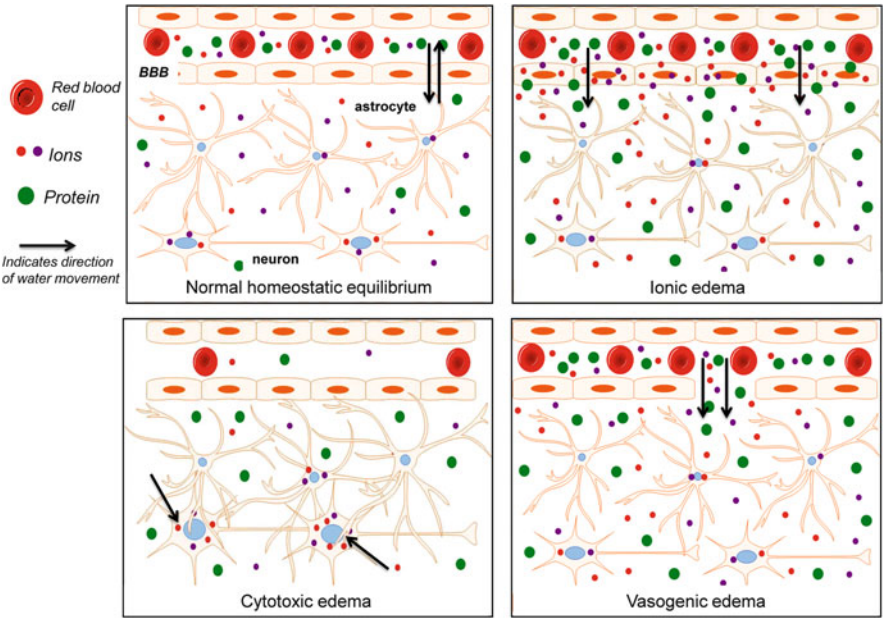


Fig. 2.2 Altered homeostasis leads to different types of edema. Note that water movements are a consequence of increased brain osmolarity due to either increased concentration of ions (BBB leakage) or loss of metabolic substrates (anoxia/ischemia)

A number of interacting mechanisms can produce cytotoxic edema after traumatic insult. However, it is chiefly the lack of nutrient (i.e., oxygen and glucose) supply to the brain and the accompanying loss of adenosine triphosphate (ATP) production that leads to a failure of neurons and glia to maintain proper ion gradients. Without ATP, the Na^+/K^+ ATPase antiporter shuts down. This results in an inadequate mechanism to rectify the passive efflux of K^+ though potassium leak channels and passive influx of Na^+ down its concentration gradient through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Following Na^+, Cl^- enters the cell via chloride channels (e.g., $Cl^-/HCO3^-$ antiporter). As the intracellular compartment has now become hyperosmotic, water flows into the cell through aquaporins causing an increase in cell volume and decrease in ECS. Swelling can lead to lysis of the cell that further exacerbates the ionic disruption and leads to necrosis [63].

Astrocytes are particularly sensitive to changes in the cerebral environment and experience greater swelling than neurons after TBI [64]. High levels of extracellular K^+ cause glutamate transporters (GLT-1 and GLAST) to reverse direction and pump K^+ into the cell and glutamate, H^+ and Na^+ out. Additionally, rat models suggest that GLT-1 and GLAST-1 are down regulated after TBI [65]. In similar fashion, high extracellular K^+ leads to upregulation of Kir 4.1 channels leading to a number of downstream effects [66]. (1) High levels of glutamate in the ECS triggers overstimulation of glutamate receptors on neurons leading to excitotoxicity

[67]. (2) Calcium entry leads to the activation of a number of enzymes (e.g., phospholipases) that cause neuronal damage or death [68]. (3) The substantial influx of K^+ via the Kir 4.1 channel on astrocytes depolarizes the cell causing entry of water [69]. The resultant cell swelling can lead to lysis of the astrocyte, which releases more glutamate and K^+ into the ECS serving to drive the cytotoxic cycle [63].

Despite the destructive environment cytotoxic edema creates for neurons and glia, the movement of water from the ECS to the intracellular compartment does not directly lead to an increase in ICP. The extracellular fluid has merely shifted into the intracellular compartment. This water uptake into cells is mediated by aquaporins. AQP4 null mice show decreased susceptibility to cytotoxic edema compared to wild-type mice [70]. However, due to ECS water loss, the fluid in the ECS has become hypertonic compared to blood. The hypertonicity of the ECS will cause the net movement of water across the BBB into the brain parenchyma [62] causing the increase in ICP.

As mentioned previously, cytotoxic and vasogenic edema rarely appear alone. The presence of both creates a cycle that serves to enhance and spread edema from the site of injury into previously unaffected areas of the brain. Cytotoxic edema, which usually appears first after TBI, will eventually cause the movement of water out of the vasculature and into the brain. Excess water increases ICP, which lowers cerebral perfusion pressure and potentiates greater cytotoxic edema. Cytotoxic edema coupled with BBB disruption (vasogenic edema) causes an influx of an even greater amount of water leading to a spreading of the edema and further decreasing perfusion leading to more cytotoxic edema.

2.8 Early Seizure After TBI

TBI produces a number of changes that lead to early seizure after TBI. Acceleration and shearing forces rupture blood vessels, sever nerve fibers and lyse cells resulting in the dysregulation of normal homeostatic processes that manifests as edema and leads to seizure. Leakage of the BBB, irrespective of mechanism, results in an increase in extracellular potassium and an increase in extracellular glutamate [16]. The increase in glutamate will cause neurons to depolarize causing a further increase in extracellular potassium.

The combined effect of BBB leakage and depolarization will lead to extracellular K^+ levels higher than the glial buffering mechanisms can compensate for. High extracellular K^+ has been shown to increase neuronal hyperexcitability by increasing the membrane potential of neurons (i.e., bringing them closer to threshold) and potentiating the influx of Na^+ [71]. As one astrocyte can regulate the environment of multiple neurons, loss of a single cell can have widespread effects. Due to this large area of dysregulation at and around the site of injury, neurons can depolarize in a synchronous manner leading to seizure.

2.9 Autoimmune Implications of BBB Disruption After TBI

One of the obstacles in clinical research on the BBB was the lack of easy to adopt and sensitive measures of its integrity. A recently developed blood test allows for the measurement of BBB function by detection of serum "reporters" of BBB function; thus, a sudden opening of the cerebrovasculature causes a rapid elevation of serum S100B level [72–75]. A number of studies have shown that S100B increase is associated with TBI. A prospective, multicenter study showed that patients with mTBI with a serum S100B measurement of 0.12 ng/mL or lower did not have intracerebral lesions and did not require cranial computer tomography [76–79]. An ironic twist in the saga related to markers of BBB dysfunction is the fact that the use of S100B has not only helped diagnose BBBD but also made it possible to elucidate one of the mechanisms that can lead to autoimmune CNS diseases. In fact, studies have shown that S100B is a powerful autoantigen upon release in systemic circulation (see below) [58].

Evidence suggests that TBI with accompanying BBB disruption leads to the formation of autoantibodies against specific neuronal antigens. The brain, similar to other barrier organs, is an immunologically privileged site [80, 81]. Accordingly, breaking the BBB and allowing what the immune system perceives as foreign antigen into the systemic environment could lead to the formation of an autoimmune response. One known example of this is sympathetic opthalmia. After traumatic insult to the eye, proteins from the eye are exposed to the immune system. As the immune system is not tolerized to eye specific proteins, an immune response can be initiated. Blindness may result in the eye affected by trauma *and* the unaffected eye [82]. A similar mechanism may underlie autoimmune diseases of the CNS.

There are a number of proposed mechanisms for the formation of anti-CNS antibodies. After injury, BBB leakage causes potential CNS antigens to enter the systemic circulation where they enter immune organs and activate autoreactive B cells. These B cells differentiate into plasma cells that begin producing the autoantibody [83]. The proinflammatory and/or necrotic events that often persist after TBI lead to drainage of potential antigens into lymphoid follicles near the area of injury. This leads to a localized production of autoantibodies [84]. Additionally, previous infection may have lead to the formation of memory B cells producing antibodies that cross react with CNS proteins. Once the BBB is breached, these antibodies are able to enter the brain and bind their target. This process has been termed "molecular mimicry" [85, 86].

TBI-associated autoantibodies have been detected against myelin-associated glycoproteins, gangliosides, and ß-tubulin III [87–89]. While no direct evidence exists to support the development of chronic autoimmune disease after TBI, it is of interest to note that a recent study has shown that the development of an autoimmune response due to frequent "openings" of the BBB and extravasation of CNS antigen is sufficient to trigger a B cell response leading to serum autoantibodies

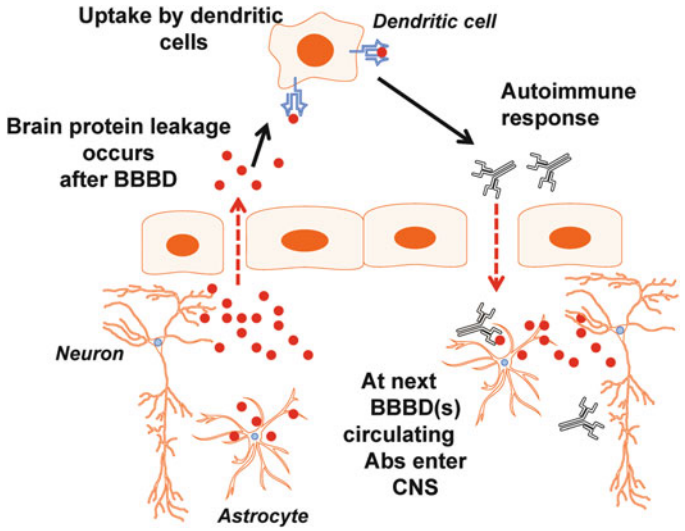


Fig. 2.3 Autoimmunity and TBI: example from football-related sub-concussive injuries [58]. Data have shown that sub-concussive head hits are accompanied by BBBD as measured by serum S100B. After release in systemic circulation, S100B is taken up by dendritic cells [92]; this leads to production of autoantibodies which may become pathogenic upon entry into the CNS

[58]. Interestingly, the authors also reported that the presence of these autoantibodies correlated with imaging and behavioral changes consistent with long-term sequelae of mTBI. Whether these autoantibodies gain entry into the CNS is yet to be demonstrated but results in epileptics show that this is a viable hypothesis (see below).

A number of anti-CNS autoantibodies are also linked to seizure (e.g., Rasmussen's encephalitis) [90]. A recently published article demonstrated that BBB disruption with seizure results in the accumulation of immunoglobulin in the cytoplasm and nuclei of neurons [91]. Whether or not this is a pathological autoimmune response, a neuroprotective response or some unknown phenomenon has yet to be determined. Animal studies and clinical data [92] have shown that a protein used as a marker of BBB disruption, astrocytic S100B, is perceived as nonself by the immune system after extravasation in blood. This protein triggers production of anti-S100B autoantibodies which may assume pathological significance. The sequelae of events linking blood–brain barrier disruption to immune dysregulation are shown in Fig. 2.3.

2.10 Conclusions

The discovery that non-neuronal mechanisms and systemic events are involved in the pathogenesis of CNS diseases is not novel. However, there is increasing evidence that this acquired knowledge may have a significant impact on how we

treat and diagnose clinical consequences of, for example, TBI. This is in particular true for seizures occurring as a consequence of TBI. A multidisciplinary (e.g., immunology-neurology), and multimodal (laboratory-preclinical-clinical) approach is necessary to bring full fruition to this research and to distribute clinical dividends of translational research in the field.

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