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Pathophysiology and Treatment of Cerebral Edema in Traumatic Brain Injury

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Abstract

Cerebral edema (CE) and resultant intracranial hypertension are associated with unfavorable prognosis in traumatic brain injury (TBI). CE is a leading cause of in-hospital mortality, occurring in >60% of patients with mass lesions, and ~15% of those with normal initial computed tomography scans. After treatment of mass lesions in severe TBI, an important focus of acute neurocritical care is evaluating and managing the secondary injury process of CE and resultant intracranial hypertension. This review focuses on a contemporary understanding of various pathophysiologic pathways contributing to CE, with a subsequent description of potential targeted therapies. There is a discussion of identified cellular/cytotoxic contributors to CE, as well as mechanisms that influence blood-brain-barrier (BBB) disruption/vasogenic edema, with the caveat that this distinction may be somewhat artificial since molecular processes contributing to these pathways are interrelated. While an exhaustive discussion of all pathways with putative contributions to CE is beyond the scope of this review, the roles of some key contributors are highlighted, and references are provided for further details. Potential future molecular targets for treating CE are presented based on pathophysiologic mechanisms. We thus aim to provide a

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translational synopsis of present and future strategies targeting CE after TBI in the context of a paradigm shift towards precision medicine.

Keywords

traumatic brain injury; cerebral edema; cytotoxic edema; ionic edema; vasogenic edema

1. Introduction

Cerebral edema (CE) can be defined as an increase in brain tissue water, including in individual cells and their surrounding interstitial space. The generation of CE after TBI is a complex heterogeneous process. Underlying mechanisms of CE may differ based on the non-modifiable nature of primary injury (etiology, velocity, force, severity, hemorrhage pattern), patient characteristics (age, sex, genetics, comorbidities), and additional clinical insults (hypoxia, hypotension, hyperthermia, seizure). A comprehensive molecular understanding of the complex networks underlying CE in TBI, although rapidly evolving, remains in its infancy. Research advances have implicated several fundamental pathophysiologic processes that contribute to edema development, including disruption of BBB integrity, cellular volume regulation by various ionic pumps, oncotic gradients and inflammatory responses (Hadass et al., 2013; Jayakumar et al., 2011; Kiening et al., 2002; Kimbler et al., 2012; Kochanek et al., 2015; Laird et al., 2014; Liang et al., 2015; Lopez-Rodriguez et al., 2015; Marmarou et al., 2006; Okuma et al., 2012; Shigemori et al., 2006; Walcott et al., 2011; Yao et al., 2015; Zweckberger et al., 2014) (Figure 1). Classically, CE after central nervous system (CNS) injury has been categorized as ‘vasogenic’ or ‘cytotoxic’, but it is increasingly recognized that these processes may be interrelated (Marmarou, 2007; Simard et al., 2007; Winkler et al., 2016). Unchecked, CE can lead to intracranial hypertension and fatal brainstem herniation. Treatment strategies aimed at removing CE after it has formed may be less beneficial than those aimed at modulating the degree and timing of activating/inhibiting the various pathways that contribute to edema formation.

2. Cerebral edema and intracranial hypertension in TBI

An important relationship between cerebral edema, intracranial hypertension, and functional outcome in TBI has been recognized for centuries. The Edwin-Smith Papyrus from the 17th century BC describes the use of neurological examinations to classify injury severity, identify intracranial hypertension and prognosticate outcome as early as 3000-2500 BC (Helgason, 1987). The use of external ventricular drains for therapeutic diversion of cerebrospinal fluid, first reported in 1744, was expanded to TBI in the 1980s, two centuries after the development of the Monro-Kellie doctrine from 1783 (Srinivasan et al., 2014). The Monro-Kellie doctrine correlates the development of CE to the practical measure of intracranial pressure (ICP) – it states that pressure within the cranial vault is a function of the volume of individual intracranial compartments (blood, brain, CSF) contained within a rigid skull/ dura matter (Macintyre, 2014). ICP elevation after TBI thus can be a product of volume increase from hematoma/contusions as well as secondary injury processes such as

CE. Although hematoma expansion is a primary concern in the first few hours after TBI, after this has been managed, CE is a major contributor to ICP elevation (Stocchetti and Maas, 2014). Intracranial hypertension can compromise cerebral perfusion pressure (CPP) and cerebral blood flow (CBF), which can eventually cause irreversible brain injury, herniation and death (Stocchetti and Maas, 2014; Winkler et al., 2016). Patients with disrupted cerebral autoregulation may be particularly vulnerable, as is often the case in TBI (Stocchetti and Maas, 2014).

Clinically, intracranial hypertension, measured by ICP monitor, has served as an evaluation and treatment proxy for CE and been a focus of guideline-based TBI care (Carney et al., 2017). Both ICP elevation and radiographic measures of CE in TBI have long been associated with unfavorable outcome in multiple cohorts (Chesnut et al., 1993; Eisenberg et al., 1990; Feickert et al., 1999; Feldmann et al., 1979; Hudak et al., 2014; Iaccarino et al., 2014; Marmarou et al., 1991; Marshall et al., 1979; Miller et al., 1977; Saul and Ducker, 1982; Stocchetti et al., 2008; Tucker et al., 2017; Vik et al., 2008). ICP elevation above the accepted threshold of 20–22 mmHg occurs in 45%–80% of patients with TBI (Marmarou et al., 1991; Narayan et al., 1982; Vik et al., 2008). There appears to be a dose-dependent effect between ICP>20 mmHg and clinical outcome after TBI (Vik et al., 2008). Preclinical studies support this strong association between CE and unfavorable outcome in TBI. Preclinical research also demonstrates that treatment of targeted pathways can reduce CE and/or improve outcome (Cao et al., 2016; Donkin et al., 2011; Fukuda et al., 2013; Gao et al., 2016; Hadass et al., 2013; Hou et al., 2018; Ruchira M Jha et al., 2018; Liu et al., 2018; McBride et al., 2014; Patel et al., 2010; Rauen et al., 2013; Shamsi Meymandi et al., 2018; Xu et al., 2016; Yang et al., 2018; Yao et al., 2015; M. Zhang et al., 2016; Zweckberger et al., 2014). In humans, no targeted therapies are clinically available. Reactive non-specific treatments such as craniectomy are invasive and carry morbidities (Stiver, 2009; Stocchetti and Maas, 2014). While decompressive craniectomy has been effective at reducing ICP and mortality in recent large randomized-controlled trials, it has an unclear benefit on functional outcome (Cooper et al., 2011; Hutchinson et al., 2016). There are similar concerns about clinical benefit despite ICP reduction with other non-specific treatments like hypothermia and hyperosmolar therapies (Andrews et al., 2015; Gottlieb and Bailitz, 2016). ICP is likely an incomplete reflection of CE, thus generalized treatment of ICP alone may not influence key pathophysiological mechanisms (Jha et al., 2018a). This underscores the importance of developing targeted therapies to expand the treatment armamentarium for CE by focusing on important molecular contributors and underlying pathways.

ICP and CPP are clinically available measures in TBI, with guidelines available to inform their management (Carney et al., 2017). Future strategies also may incorporate individual measures of intracranial compliance, pressure reactivity indices (PR_x), pulse amplitude index (PA_x) and optimal-cerebral perfusion pressure (CPP_{OPT}) that are currently of research interest. While a focus on these measures is beyond the scope of this review, a brief summary is provided below with references available for further review.

Not explicitly factored into the Monro-Kellie doctrine is the concept of an individual's intracranial compliance and elastance which affect the degree of ICP elevation. While difficult to measure clinically, quantifying individual cerebral compliance ($\Delta V/\Delta P$) or its

inverse, i.e., elastance ($\Delta P/\Delta V$), could be useful to predict impending ICP crises and herniation (Czosnyka and Citerio, 2012; Howells et al., 2012). Originally described by Marmarou *et al.* in a cat model, the pressure volume index (PVI) was one of the first measures of intracranial elastance (Czosnyka et al., 2012; Marmarou et al., 1975). PVI is the volume (mL) required to raise ICP 10-fold and is normally 20-25 mL ($PVI \text{ (mL)} = V/\log(P_p/P_o)$) where V = volume in mL, P_p = peak ICP, and P_o = ICP prior to volume change (Marmarou et al., 1978; Shapiro et al., 1980). Despite its potential utility, PVI is technically challenging, carries an infection risk, and may precipitate ICP crises (Hawthorne and Piper, 2014). Research efforts have largely been redirected towards indirect measures of cerebral compliance such as ICP waveform/amplitude analysis and MRI based quantification (Alperin et al., 2000; Atsumi et al., 2014; Czosnyka and Citerio, 2012; Howells et al., 2012; Raksin et al., 2003). Similarly, measures of cerebrovascular reactivity such as the PRx, PAX and CPP_{OPT} are ongoing research interests with the goal of eventually directing precision-medicine based treatment for ICP and/or CPP targets and optimal blood flow (Dias et al., 2015; Zeiler et al., 2018, 2017). PRx, a dynamic correlation coefficient (-1 to +1), is obtained from a 5-second average of 40 consecutive measurements of mean arterial pressure (MAP) and ICP. With intact autoregulation, an increase in MAP results in vasoconstriction, thus reducing ICP (negative PRx); conversely, absent pressure reactivity results in ICP passively following MAP (positive PRx) (Zweifel et al., 2008). CPP_{OPT}, has been defined as the point of lowest PRx – a value that may differ not only between individual patients, but also within the same patient at different times (Steiner et al., 2002). PAX is the ICP pulse amplitude index given by the Pearson correlation coefficient between MAP and ICP pulse amplitude (Zeiler et al., 2017). As intracranial elastance increases (compliance decreases), ICP pulse amplitude increases (Hawthorne and Piper, 2014). In research studies, these measures are predictive of outcome and may be manipulable; however they are yet to be validated for clinical/guideline-based care (Dias et al., 2015; Zeiler et al., 2017; Zweifel et al., 2008).

The measures described above are all focal reflections of a diffuse, multifaceted, heterogeneous and dynamic process. In an evolving world of precision-medicine, it may be prudent to complement these measures with other forms of multimodal monitoring, imaging studies, phenotypic and genetic biomarkers to provide a nuanced and mechanistic approach to understanding and ultimately treating CE in TBI (Jha and Kochanek, 2017).

3. Pathways involved in ionic and cellular/cytotoxic edema (CytE)

Cytotoxic edema (CytE) results from ionic pump failure or activation of select ion channels, with ensuing loss of homeostatic ionic gradients. This causes cellular swelling wherein water moves from the interstitial to intracellular space (Hudak et al., 2014; Winkler et al., 2016). It has been reported as early as 1 hour post-TBI in humans (Ito et al., 1996). Cellular edema can occur in all CNS cell types, including astrocytes, endothelial cells and neurons; it has been carefully characterized in astrocytes (Stokum et al., 2016). Isolated cellular swelling does not increase total brain water, since it is a redistribution of water from the interstitial to the intracellular space. A true increase in brain water content requires perfusion from an external fluid source, which is debated to be the cerebral vasculature (driven by osmotic forces), and/or the glymphatic system (due to enhanced cerebrospinal-fluid (CSF)

influx or impaired efflux); importantly, these hypotheses are not mutually exclusive (Iliiff et al., 2014; Stokum et al., 2016; Thrane et al., 2014). If unrestrained, ionic failure and resultant cellular edema becomes cytotoxic and leads to cell death (Hudak et al., 2014; Simard et al., 2007). Ionic edema is analogous to CytE of endothelial cells, but there is a polarity to transcapillary ion and water fluxes. A continuum of CytE, ionic edema, vasogenic edema (VasE), and progressive secondary hemorrhage (PSH) is illustrated in Figures 2-5 (Simard et al., 2007). As described below, many of these pathways and their components are inter-connected.

3.1. $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter (NKCC1)

NKCC1 is a $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter expressed constitutively in neurons, glia, capillary and choroid-plexus endothelial cells (J. Zhang et al., 2017). Normally, NKCC1 uses the electrochemical gradient generated by the $\text{Na}^+\text{/K}^+\text{/ATPase}$ to mediate transport of Na^+ , K^+ , 2X Cl^- ions (with water co-transport) across the plasmalemma, thus regulating cell volume and ion homeostasis (J. Zhang et al., 2017). In preclinical TBI models, NKCC1 is upregulated as early as 1 hour post-injury and is activated by a variety of mechanisms including increased extracellular K^+ (after $\text{Na}^+\text{/K}^+\text{/ATPase}$ failure, particularly in astrocytes), $\text{IL-1}\beta$, and glutamate (*see* Sections 2.5 and 3.1) (Jayakumar et al., 2011; Lu et al., 2006, 2008, 2017; Simard et al., 2010; J. Zhang et al., 2017; M. Zhang et al., 2016). Transporter activation after TBI results in elevated intracellular ionic content and water, i.e., CytE. In CNS endothelial cells, NKCC1 is expressed primarily on the luminal side, thus contributing to cellular edema loading Na^+ into cells (Simard et al., 2010). Some *in vivo* data suggest a link between this pathway and AQP4 upregulation after controlled cortical impact (CCI) (*see* Section 2.2), as well as matrix-metalloproteinase (MMP)-9 production (*see* Section 3.5) and BBB integrity (J. Zhang et al., 2017; M. Zhang et al., 2016). NKCC1 activation also may trigger a mitogen-activated protein kinase cascade, further increasing CE and neuronal damage after TBI (Lu et al., 2017, 2008).

3.2. Aquaporins (AQP)

AQPs likely influence both cellular/CytE and VasE in TBI. In the CNS, AQP1 and AQP4 are most prevalent (Papadopoulos and Verkman, 2013). AQP1, involved in CSF secretion, is primarily expressed in the ventricular-facing plasmalemma of choroid plexus epithelium; it is absent from cerebrovascular endothelium (except in circumventricular locations lacking a BBB) (Papadopoulos and Verkman, 2013). AQP4 localizes to brain-fluid interfaces including perivascular astrocyte endfeet, glia limitans, basolateral membrane of ependymal cells and subependymal astrocyte processes. In CytE, water enters the CNS through AQP4 on perivascular astrocyte foot-processes. In VasE, water is eliminated via AQP4 via different routes: astrocyte foot-processes into the blood stream, subpial astrocyte processes and pial cells into subarachnoid CSF, and across subependymal astrocyte processes and ependymal endothelium into the ventricle, the glymphatic system (Filippidis et al., 2016; Hubbard et al., 2018; Iliiff et al., 2014). The M23 AQP4 isoform associates in membranes as a tetramer, and can aggregate into orthogonal arrays of particles (supramolecular assemblies) (Papadopoulos and Verkman, 2013).

In TBI, since there are contributions from both CytE and VasE, determining the overall contribution of AQP4 to edema formation versus elimination has been challenging and may be related to spatial/temporal expression patterns. TBI studies have shown AQP4 downregulation for up to 48 hours after TBI (potentially coinciding with VasE), some of which occurs specifically in regions with BBB disruption (Cartagena et al., 2014; Ke et al., 2001; Kiening et al., 2002; Liu et al., 2015; Zhang et al., 2015). Other studies have shown AQP4 upregulation coinciding with CytE development within 72 hours (Lopez-Rodriguez et al., 2015; Lu et al., 2013; Taya et al., 2010). A study in murine closed head injury demonstrated that, while there was a global increase in cortical and striatal AQP4 expression (peak at 7 days), perivascular AQP4 expression was markedly reduced by day 3 (persisting until day 28) (Ren et al., 2013). While not clearly noted, this suggests that changes in AQP4 localization/loss of polarization, while potentially worsening VasE (by limiting water clearance), may be a compensatory mechanism to counteract/decrease CytE (Ren et al., 2013). A subsequent study in mild-CCI demonstrated that astrocytic foot-process edema was reduced in AQP4^{-/-} mice (from decreased CytE); however, the effects were smaller than AQP4 deletion in models of pure CytE, likely a consequence of the decreased AQP4-dependent clearance of VasE (Yao et al., 2015). Increased AQP4 expression has been reported in human TBI tissues, and CSF levels are significantly higher in patients with severe TBI versus controls. Further studies are warranted to evaluate the impact on edema (Hu et al., 2005; Lo Pizzo et al., 2013).

3.3. Sulfonylurea-Receptor 1 – Transient Receptor Potential member 4 (Sur1- Trpm4)

Sulfonylurea receptor 1 (Sur1) co-assembles with various pore-forming subunits (e.g., Kir6.2, Trpm4) to form hetero-octameric channels. The association of Sur1 with the non-selective cation channel Trpm4, and the relationship of this channel to CytE was first described in ischemic stroke, and has since been characterized in other CNS diseases including TBI (Patel et al., 2010; Simard et al., 2006, 2009, 2012b). Unique to this pathway, the Sur1-Trpm4 channel is not normally expressed in the CNS but is transcriptionally upregulated by injury, thus rendering it an ideal target for therapeutic intervention. Unlike NKCC1, intracellular ATP depletion activates Sur1-Trpm4, promoting channel opening, sodium influx, cell depolarization, blebbing, and cellular/cytotoxic death. In TBI, Sur1 is upregulated in endothelial capillaries, astrocytes and neurons (Patel et al., 2010; Simard et al., 2009). Neuronal or astrocytic increases in Sur1-Trpm4 result in CytE and eventually oncotic death of these cells. Luminal Sur1-Trpm4 expression in endothelial cells contributes to ionic edema, and eventually cytotoxic/cellular edema of the endothelial cells. This further contributes to VasE, as the endothelial cells continue to swell and tight junctions between them are degraded, thereby transforming capillaries into ‘fenestrated’ capillaries that allow proteinaceous fluid extravasation (Kurland et al., 2012; Stokum et al., 2016). In its extreme form, capillary/BBB integrity is lost, resulting in PSH (Figure 5) (Kurland et al., 2012; Simard et al., 2007). Thus, CytE, VasE and PSH may represent a continuum of CE in TBI.

Human CSF Sur1 is elevated in TBI versus controls, and correlates with CE (Jha et al., 2017a). Sur1 overexpression has also been demonstrated in post-traumatic human contusions, particularly in neurons and endothelial cells (Martínez-Valverde et al., 2015). Polymorphisms in the Sur1 gene (*ABCC8*) have been associated with increased risk of CE

(Jha et al., 2017b; Ruchira Menka Jha et al., 2018b), which may have important implications for precision medicine patient risk-stratification, therapeutic response, and selection for clinical trials. A recent study demonstrated a tripartite-complex association between Sur1-Trpm4-AQP4 (Stokum et al., 2018). While this has not been demonstrated in TBI, it has important implications for the pathophysiology of edema generation and interconnections between contributory pathways.

3.4. Acid sensing ion channel (ASICs), Na⁺/H⁺ exchanger (NHE), Na⁺/HCO₃⁻ transporter family channel (NBC)

ASICs are upregulated and activated by extracellular H⁺, and open to inwardly conduct Na⁺ (some subunits, e.g., ASIC1a, also conduct Ca²⁺) (Gu et al., 2010; Xiong et al., 2004; Yermolaieva et al., 2004; Yin et al., 2013; Zhao et al., 2008). In the CNS, ASIC1a and ASIC2 heterotrimers are the most widely expressed. In human cortical neurons, the pH required for half maximal activations is 6.60 (Li et al., 2010). Channel opening and Na⁺ influx causes cell depolarization and an increase in water content resulting in cell swelling. Glutamate receptor-independent Ca²⁺ entry via these channels also contributes to excitotoxicity and apoptosis. Other constitutively expressed pH-regulated channels (NHE, NBC) activated by an interstitial pH ≤6.8, also mediate astrocytic swelling *in vitro*; however their contribution to CytE in TBI *in vivo* has not been established (Stokum et al., 2016).

3.5. Glutamate

After TBI, glutamate excitotoxicity has both deleterious effects on secondary injury cascades (including CE) as well as a later beneficial impact on neuronal survival (Chodobski et al., 2011). Early after injury, extracellular glutamate concentrations may rise beyond 200 μM (synaptic release, cellular/neuronal lysis, spreading depolarization) (Stokum et al., 2016); even 5–50 μM can induce astrocytic edema via the constitutively expressed EAAT1/2 channels. In normal brain, EAAT2 forms a multiprotein-complex with AQP4, and contributes to glutamate uptake and homeostasis. Elevated glutamate levels after injury mediate the influx of glutamate via EAAT1/2 expressed on astrocytes, with co-transport of Na⁺ and water, thus inducing astrocytic CytE (Stokum et al., 2016). Glutamate can also contribute to CytE through its ionotropic NMDA-receptor, leading to intracellular influx of Na⁺ and Ca²⁺ (Winkler et al., 2016). *In vitro* experiments suggest that glutamate acting through metabotropic receptors also may increase BBB permeability (Chodobski et al., 2011; Collard et al., 2002). Glutamate may induce brain endothelial apoptosis through increased production of nitric oxide and reactive oxygen species; however, this is controversial (Domoki et al., 2008; Parfenova et al., 2006, 2003).

3.6. Arginine Vasopressin

Arginine vasopressin (AVP), a nonapeptide produced by the paraventricular and supraoptic hypothalamic nuclei, is upregulated after TBI (Krieg et al., 2017; Winkler et al., 2016). The V_{1a} receptor, widely distributed in neurons, astrocytes and endothelial cells, is also upregulated perilesionally after injury (Krieg et al., 2017; Marmarou et al., 2014; Pascale et al., 2006). Both genetic and pharmacologic inhibition in TBI models has successfully reduced CytE (Kleindienst et al., 2013; Krieg et al., 2017, 2015; Pascale et al., 2006; Rauen et al., 2013). The mechanism of V_{1a}-mediated CytE is unknown but is hypothesized to be

related to modulation of parenchymal vasopressin regulation of AQP4 expression and function (Filippidis et al., 2014). Modulation of V_{1a} in rats has shown an impact on brain extracellular Na^+ concentrations and ICP; however, this has not been demonstrated in humans (Allen et al., 2018; Filippidis et al., 2014).

3.7 Commentary on molecular candidates contributing to CytE

There has been an exponential growth in literature identifying various pathways contributing to different cerebral edema subtypes. The candidates discussed in this subsection on ionic and CytE were selected for inclusion based on research and evidence specifically in TBI, with the most promising candidates being presented based on multiple studies performed by more than one laboratory group. Given the connective network between many of these molecular targets such as NKCC1, glutamate, AQP4, and Sur1-Trpm4 (Stokum et al., 2018; J. Zhang et al., 2017; M. Zhang et al., 2016), it is difficult to isolate a selective hierarchy of importance among these with the information available at this stage. There is also overlap between some of these molecular components and those involved in VasE (e.g., MMP-9; see Subsection-4). Identification of targets that are inter-related (or even inter-dependent), suggests their relative importance in the underlying pathophysiology of CE versus more apparently isolated targets such as vasopressin, NHE, NBC. Indeed, it is possible that a multi-targeted approach may eventually be most beneficial and should be evaluated in preclinical and clinical studies. While the authors' biases towards NKCC1, AQP4, Sur1-Trpm4 and MMP-9 are based on available evidence both in terms of individual studies as well as their potential inter-relatedness, it is important to remain cautious since connections between pathways and other molecular targets may exist but are currently unknown. As discussed in Subsection-5, of the targets outlined, the only one that to date has shown promise in a prospective *human* randomized trial of TBI is Sur1-Trpm4, where glibenclamide decreased contusion expansion (Khalili et al., 2017); results from another clinical trial evaluating glibenclamide (NCT01454154) are pending. Strategies against AQP-4 and NKCC1 while promising have not yet been assessed for clinical relevance in human TBI studies.

4. Pathways involved in BBB disruption and vasogenic edema

One of the first contributors to BBB breakdown in TBI is immediate mechanical disruption after primary injury (Figure 1). Contusional edema is generated from an osmotic potential across central necrotic tissue (high osmolality) and surrounding brain (Katayama et al., 1998; Katayama and Kawamata, 2003). Katayama *et al.* initially characterized this pattern of edema in animals by measuring contusion and peri-contusional osmolality and water content (Katayama et al., 1998). They confirmed this in patients using apparent diffusion coefficient imaging (Ito et al., 1996; Katayama et al., 1998; Katayama and Kawamata, 2003). Mechanical disruption, although the most immediate cause, is not the sole etiology of BBB breakdown; second messenger cascades including proinflammatory cytokines/ neuroinflammation, angiogenic factors, tight junction degradation, adhesion molecules/ factors promoting protein extravasation and cytoskeletal rearrangements are some of the additional factors contributing to a leaky endothelium/VasE that may peak between 6–24 hours (Figure 2) (Winkler et al., 2016). Proteinaceous fluid leaking into the interstitial space

may further increase oncotic pressure and occlude small vessels, causing local hypoperfusion/ischemia that can exacerbate ionic failure/CytE (Stocchetti and Maas, 2014; Winkler et al., 2016). Maximal BBB permeability has been noted within the first few hours post-injury in different TBI models, and can persist for 3–4 days (Readnower et al., 2010; Shetty et al., 2014; Tanno et al., 1992; Whalen et al., 2000b; Yeoh et al., 2013). A second peak in BBB breakdown may occur after 5 days, which is thought to be mediated by microglial activation (Readnower et al., 2010; Winkler et al., 2016). Historically, CE in TBI was thought to be primarily vasogenic, but cytotoxic edema has now been shown to be a significant contributor (Barzó et al., 1997; Hudak et al., 2014; Marmarou et al., 2006; Winkler et al., 2016). While an earlier study (44 subjects) found a predominance of cellular edema post-TBI, a recent study (97 subjects) showed a more even split with 46% of patients demonstrating predominantly CytE and 54% with predominantly VasE (Hudak et al., 2014; Marmarou et al., 2006). The predominant edema type may indeed be highly dependent on the individual patient based on the injury phenotype, genetics, as well as secondary insults and treatments provided.

4.1. Inflammatory cytokines

Neuroinflammation after TBI is a multifaceted process implicated in both secondary injury and repair/ recovery (Jassam et al., 2017; Simon et al., 2017). Both primary and secondary injury result in the release of damage associated molecular patterns (DAMPs) that, in turn, activate networks of cells (glia, neurons, endothelial cells, leukocytes) to induce inflammatory gene expression, guiding the ensuing immune response (Jassam et al., 2017). This includes upregulation and release of cytokines such as tumor necrosis factor (TNF) and interleukins (IL) 6 and 1 β , which are early mediators of post-traumatic inflammation (Simon et al., 2017). The mechanisms by which pro-inflammatory cytokines induce BBB dysfunction are many, and are still being elucidated. Reported pathways include increased MMP expression (Alluri et al., 2016; Guilfoyle et al., 2015; Hadass et al., 2013; Rosenberg and Yang, 2007), leukocyte/neutrophil recruitment with subsequent loss of tight junctions (Bolton et al., 1998), production of permeability-increasing molecules (bradykinin, substance P) (Walker et al., 1995), increased chemokine synthesis, expression of inflammatory cell adhesion molecules (intracellular adhesion molecule (ICAM)/vascular cell adhesion molecule) and recruitment of other systemic inflammatory cells (Chodobski et al., 2011; Winkler et al., 2016). One reported cascade involves HMGB1 binding to TLR4, which upregulates IL-6; this in turn leads to astrocytic upregulation of AQP4 and VasE (Laird et al., 2014). While there is some support for this pathway influencing outcome in humans, its role in the development of CE remains to be characterized (Au et al., 2012). Another key pro-inflammatory cytokine, TNF, has been shown to promote actin stress fiber formation followed by endothelial cell retraction (and formation of intracellular gaps mediated by myosin light chain kinase MLCK), as well as downregulating the tight junction protein, occludin (Bolton et al., 1998; Chodobski et al., 2011; Mankertz et al., 2000; Wójciak-Stothard et al., 1998); however, these actions have yet to be demonstrated in TBI models.

While early pro-inflammatory cytokines are themselves associated with BBB disruption, they also induce additional cytokines such as tumor growth factor (TGF) β , which further compromise BBB integrity (Morganti-Kossmann et al., 1999). *In vitro* studies demonstrated

a dose-dependent effect of increasing TGF- β levels on paracellular permeability of brain endothelial monolayers, thought to be due to decreased expression of VE-cadherin and the tight junction protein, claudin-5 (Shen et al., 2011). In 22 patients, elevated CSF TGF- β levels were associated with increased BBB permeability (Morganti-Kossmann et al., 1999). IL-8, another upregulated cytokine in glia and endothelial cells, increased BBB permeability in animal and human studies. In children, high CSF IL-8 levels were associated with mortality; in adults, this was associated with BBB permeability but not mortality (Buttram et al., 2007; Helmy et al., 2011; Maier et al., 2001; Whalen et al., 2000a). Elevated CSF complement levels (C3 and factor B), peaking 24 hours post-injury and declining on days 2–7, also have been associated with BBB dysfunction after TBI (Kossmann et al., 1997; Stahel et al., 2001).

4.2. Chemokines

Elevated chemokine levels have been demonstrated in many TBI models (Woodcock et al., 2017). Early after TBI, chemokines appear to be synthesized by astrocytes and the cerebrovascular endothelium, with later contributions from invading neutrophils and monocytes (Chodobski et al., 2011). Commonly studied chemokines in TBI include chemokine (C-X-C motif) ligands CXCL1 and CXCL2 (neutrophil attractants), and chemokine (C-C motif) ligand CCL2, which induces a chemotactic response in macrophages, monocytes and microglia (Woodcock et al., 2017). In addition to recruiting leukocytes after TBI, chemokines also may increase BBB permeability via mechanisms similar to cytokines. For example, CCL2 induces the formation of actin stress fibers and causes redistribution of claudin5, occludin, and zona-occludens (ZO) 1 and 2 (Chodobski et al., 2011; Stamatovic et al., 2003; Woodcock et al., 2017). As with the balance in neuroinflammation between pro/anti-inflammatory cytokines, atypical chemokines (e.g., ACKR2) also serve as scavengers that internalize and promote degradation of proinflammatory chemokines (Woodcock et al., 2017).

4.3. Inflammatory cells

Migration of peripheral and brain-resident inflammatory cells to the site of injury in TBI can be both beneficial and maladaptive (Corrigan et al., 2016; Simon et al., 2017). In focal injury, there is an early microglial response and neutrophilic infiltration within the injury site (Jassam et al., 2017; Simon et al., 2017). Migration of monocytes, lymphocytes and astrocytes occurs later (Corrigan et al., 2016). In diffuse injury, there is minimal neutrophil infiltration, and the early cellular response (seen primarily in white-matter tracts) consists of microglia and astrocytes (Corrigan et al., 2016). In animal models, cerebrovascular endothelium in the injured hemisphere increases expression of neutrophilic vascular adhesion molecules (E-selectin, ICAM-1) within 4 hours, thus facilitating migration of these peripheral immune cells beyond the BBB (Simon et al., 2017). In stroke, neutrophilic release of elastase and MMPs has been shown to compromise BBB integrity and result in CE (Ikegame et al., 2010; Kenne et al., 2012; Morancho et al., 2010). While this effect of neutrophils in TBI remains controversial, there are recent data in CCI to suggest that neutrophil depletion reduces CE, microglial activation, and caspase-3 (Jassam et al., 2017; Kenne et al., 2012). Antagonism of neutrophil elastase was beneficial in attenuating VasE as well as cell death in CCI (Semple et al., 2015b). Activation of M1-like microglia by

proinflammatory cytokines and chemokines is thought to increase BBB permeability by activating MMPs and modulating proteins essential to tight junction formation (Corrigan et al., 2016; da Fonseca et al., 2014).

4.4. Vascular endothelial growth factor A (VEGF-A)

VEGF-A, a secreted glycoprotein, is critical for angiogenesis and also increases microvascular permeability (Chodobski et al., 2011). It is normally expressed in neurons, astrocytes, ependymal cells, and the pial/glial lining. VEGF-A binds to two major receptors: VEGF-receptor (R)-1 (a tyrosine kinase), and VEGFR-2 (kinase domain insert receptor). VEGF-A is upregulated in astrocytes and the cerebrovascular endothelium rapidly after TBI in preclinical models and in human tissues (Chodobski et al., 2003; Suzuki et al., 2003). *In vitro* (brain and endothelial cells), a VEGF-A-dependent increase in brain endothelial cell permeability is mediated by VEGFR1; mechanisms reported include downregulation and/or ubiquitination of the tight junction proteins, occludin and claudin-5 (Argaw et al., 2009; Murakami et al., 2009; Wang et al., 2001). Like MMP-9 (*see* Section 3.5) and many other mediators of BBB permeability, VEGF also plays a role in neurogenesis and repair; post-TBI treatment with exogenous VEGF had been shown to decrease lesion volume and improve functional outcomes (Thau-Zuchman et al., 2010). These effects may differ temporally, whereby early VEGF expression disrupts the BBB but later is required for neural repair. Of note, MMP-9 processes and activates pro-VEGF and matrix-bound VEGF, one of many examples showing that pathways of CE are often highly interconnected networks, not stand-alone targets (Zhao et al., 2006).

4.5. Matrix metalloproteinase (MMP)

MMPs, a family of zymogens, have been extensively implicated in BBB pathophysiology due to their role in extracellular matrix degradation, as well as regulation of (and induction by) cytokines and chemokines. In TBI, MMPs can be activated by oxidative stress, cytokines, chemokines, infiltrating or resident inflammatory cells, neurons and endothelial cells (Winkler et al., 2016). They are regulated by endogenous inhibitors (tissue-inhibitors of metalloproteinases) (Chodobski et al., 2011). MMP-2 and MMP-9, the most abundantly expressed CNS MMPs, have been the most studied regarding their impact on BBB integrity. A small prospective study in severe human TBI revealed the earliest appearance of MMPs 8 and 9 was at 12–18 hours, followed by MMP-2 (detection 30–35 hours, peak 42–48 hours) (Roberts et al., 2013).

MMP-2 is a gelatinase (type-IV collagenase), predominantly expressed in normal astrocytes (Sharma et al., 2017). It is tethered to the cell surface, thus restricted in its proteolytic reach (S. Zhang et al., 2016). MMP-2 upregulation post-TBI has been noted within 72 hours in animal and human studies, and is associated with ultrastructural changes in endothelial cells and perivascular hemorrhage reflecting BBB disruption (Guilfoyle et al., 2015; Vajtr et al., 2009; Vilalta et al., 2008; S. Zhang et al., 2016).

MMP-9 is released into the extra-cellular space and can have effects distant from the site of release (S. Zhang et al., 2016). Neutrophils are a primary source of MMP-9, but it is expressed in other invading leukocytes, endothelial cells, and also weakly in astrocytes and

neurons (Chodobski et al., 2011; Zhao et al., 2006). A study in 12 patients demonstrated elevated MMP-9 microdialysate levels in peri-contusional tissue at ≤ 72 hours. No differences in any of the other MMPs studied (1, 2, 7, 10) were noted between injured versus “normal”/contralateral brain. This, combined with prior reports of CSF MMP-9 levels, suggests its potential utility as a biomarker (Guilfoyle et al., 2015; Nwachuku et al., 2016; Roberts et al., 2013). In human studies of stroke, serum MMP-9 levels correlate with BBB disruption and malignant edema (Jha et al., 2014; Kimberly et al., 2014; Serena et al., 2005; Sheth et al., 2016; Simard et al., 2012a). In a recent clinical stroke trial, MMP-9 levels were lower in glibenclamide-treated subjects, who also had less radiographic midline shift, a measure of CE (Sheth et al., 2016). Glibenclamide inhibits Sur1-Trpm4, and is also an indirect MMP-9 inhibitor (Simard et al., 2012a).

4.6. Substance P (SP)

SP, a tachykinin, is a potent contributor to neurogenic inflammation due to its association with increased vascular permeability, promotion of leukocyte chemotaxis, and activation of astrocytes and microglia to produce proinflammatory cytokines via pathways involving nuclear factor κ B (NF- κ B), all of which increase BBB disruption (Corrigan et al., 2016; Donkin et al., 2009; Lorente et al., 2015). In the CNS, SP is contained in sensory nerve fibers (densely surrounding cerebral arteries) (Corrigan et al., 2016). SP effects are predominantly mediated by tachykinin (neurokinin; NK) receptors (preferentially NK1 expressed on endothelial cells, astrocytes, microglia, and other immune cells). These are G-protein receptors that regulate ion channel and enzyme activity as well as gene expression (Corrigan et al., 2016). In preclinical and clinical TBI studies, SP levels are elevated early, and are detectable in plasma (Donkin et al., 2009; Lorente et al., 2015; Zacest et al., 2010). One human TBI study (23 subjects) demonstrated increased SP immunoreactivity perivascularly and in neurons and astrocytes (Zacest et al., 2010). A second study (100 subjects), demonstrated correlations between plasma SP elevation and unfavorable outcome and mortality, but not with ICP (Lorente et al., 2015).

4.7. Commentary on molecular candidates contributing to VasE

Akin to the discussion in subsection 3.7 regarding candidates contributing to CytE, it is challenging to identify the relative importance of individual VasE targets/pathways, particularly given the dearth of evidence in TBI. Nonetheless, it is an important area for future research. One may speculate that candidates with evidence of inter-relatedness with other targets and across different pathways are likely to have a more significant impact on CE generation. Many of the candidates presented here meet this criterion. For example, Sur1-Trpm4 and AQP-4 have a reported inter-connectedness; both of these contribute to CytE and VasE, and appear to overlap with pathways involving MMP-9 (Amtul et al., 2018; Gerzanich et al., 2018; Lee et al., 2014; Sheth et al., 2016; Stokum et al., 2018). Proinflammatory cytokines and chemokines activate MMP-9, which in turn modulates VEGF (Corrigan et al., 2016; da Fonseca et al., 2014; Zhao et al., 2006). All of these also are linked independently to BBB breakdown and VasE. It is thus possible that analogous to various chemotherapeutic regimens, a multi-pronged treatment approach targeting Sur1-Trpm4, AQP4, VEGF and MMP-9 may be more potent than a single-targeted approach. Such questions may be beneficial to explore in different TBI models, especially in terms of

optimizing timing and dose of the various therapies, and evaluating combined toxicity profiles.

5. Targeting cerebral edema in TBI

Current clinical management of CE is targeted towards reducing ICP and maintaining cerebral perfusion pressure, as outlined in the Brain Trauma Foundation guidelines (Carney et al., 2017). These therapies (such as hyperosmolar treatment, sedation, neuromuscular blockade, hypothermia, and craniectomy) are non-targeted, reactive, and have significant side effects. This section discusses some promising molecular candidates targeting the underlying pathophysiology of CE presented earlier that, if successful, may allow clinicians to limit the use of non-targeted therapies.

5.1. Pharmacologic agents targeting cellular swelling

Whether cellular swelling is cytotoxic versus protective in TBI remains unclear, and the two may lie on the same continuum depending on the degree, timing, and location. What is clear, is that this process plays a significant, possibly dominant, role in many TBI patients (Hudak et al., 2014; Marmarou et al., 2006). This section summarizes many promising strategies targeting pathways discussed in Section 2, that are at various stages of development (Table 1). Many of the same molecules influence both cellular swelling and BBB disruption.

5.1.1. Bumetanide—Bumetanide inhibits NKCC1 and reduces astrocytic swelling in vitro after fluid percussion injury (FPI) (Jayakumar et al., 2018, 2011). In vivo TBI models have shown reductions in cellular swelling and BBB disruption (Lu et al., 2006, 2008, 2017; Simard et al., 2010; J. Zhang et al., 2017; M. Zhang et al., 2016). Given the mechanistic and temporal differences in NKCC1 and Sur1-Trpm4 contributions to CE (see Sections 2.1 and 2.3), therapeutic synergy between bumetanide and glibenclamide has been proposed (Simard et al., 2010). Currently, there are no studies of this drug in human TBI but it is being evaluated in neonatal seizures (ClinicalTrials.gov NCT00830531).

5.1.2. AER-271 and Aquaporumab—AQP-4 inhibition in vivo (knockout, RNA-interference) has shown mixed results, with many studies showing edema amelioration and a few showing no-effect/potential worsening (Chen et al., 2016; Fukuda et al., 2013; Higashida et al., 2011; Kiening et al., 2002; Ren et al., 2013; Yao et al., 2015). AQP4^{-/-} mice have reduced edema in models of relatively pure CytE (cerebral ischemia, water intoxication), suggesting a role for AQP4 in CytE generation, but worse edema in models with predominantly VasE (tumors, subarachnoid-hemorrhage, abscesses) (Manley et al., 2000; Papadopoulos et al., 2004; Papadopoulos and Verkman, 2013), indicating the potential importance of AQP4 in elimination of VasE (Filippidis et al., 2016; Hubbard et al., 2018; Iliff et al., 2014). Uninjured AQP^{-/-} mice have normal ICP and minimally increased brain water content, suggesting that slow water fluxes can occur independently of AQP4 (Papadopoulos and Verkman, 2013). AER-271 is a selective AQP-4 antagonist that showed a trend towards decreased ICP in a combined model of CCI and hemorrhagic shock; surprisingly, however, it did not reduce brain water (Wallisch et al., 2015). Aquaporumab, a monoclonal AQP-4 specific antibody, has been utilized to reduce neuromyelitis optica

pathology in vivo, but has not been evaluated in TBI (Papadopoulos and Verkman, 2013). No human studies have been reported.

5.1.3. Glibenclamide (glyburide)—Glibenclamide binds to Sur1 (EC50 48 nM at pH 7.4) and blocks the Sur1-Trpm4 channel by prolonging and increasing the probability of the channel's long-closed state without affecting conductance (Chen et al., 2003; Simard et al., 2014). Its potency is increased eight-fold in acidic environments (pH 6.8), which may be encountered in injury states due to lactic acidosis. In an acidic milieu, glibenclamide's ability to cross the BBB is also enhanced; thus, it may be selectively taken up in distressed CNS microenvironments (Simard et al., 2014). In preclinical TBI models, glibenclamide (at various doses/durations) reduced regional edema, ICP, PSH, BBB disruption, and neurologic dysfunction (R. Jha et al., 2015; R. M. Jha et al., 2015; Patel et al., 2010; Simard et al., 2009; Xu et al., 2016; Zweckberger et al., 2014). Glibenclamide is being evaluated in a clinical TBI trial (ClinicalTrials.gov NCT01454154, results pending). A Phase-II trial in stroke has shown promising results, decreasing edema measured by midline-shift. In a recent RCT (40 subjects), glibenclamide improved outcomes after moderate-to-severe diffuse axonal injury; however, an effect on edema was not evaluated (Zafardoost et al., 2016). Another RCT (66 subjects) demonstrated that glibenclamide reduced contusion expansion but did not influence clinical outcome in moderate-to-severe TBI (Khalili et al., 2017).

5.1.4. Amiloride—Amiloride inhibits NHE-1 and ASIC1a and was neuroprotective in a preclinical TBI study, as well as other neurologic diseases (Arun et al., 2013; Durham-Lee et al., 2011; Stankowska et al., 2018; Tai and Truong, 2013; Zhao et al., 2008). Its effect on edema has not been well explored but one report in a weight-drop model suggested an ameliorative effect (Vaz et al., 1998). No human studies have been reported.

5.1.5. SR 49059, V1880, Conivaptan and vasopressin— *Genetic and pharmacologic inhibition of V_{1a} receptors reduces CytE in vivo (Kleindienst et al., 2013; Krieg et al., 2017, 2015; Pascale et al., 2006; Rauen et al., 2013). SR 49059 is a small molecule selective V_{1a} receptor antagonist, and V1880 is a peptide selective V_1 receptor antagonist. Both agents reduce CytE and ICP in preclinical TBI models (Krieg et al., 2017, 2015; Marmarou et al., 2014; Rauen et al., 2013). In a pilot RCT (10 subjects) with randomization to Conivaptan (V_{1a} and V_2 antagonist) versus standard-of-care, ICP was lower in the treatment arm ($p=0.046$) with a concomitant increase in serum Na^+ ($p=0.02$) (Galton et al., 2011). Conversely, human studies evaluating vasopressin (an AVP agonist) in severe TBI have not shown ICP increases or CE exacerbation (Allen et al., 2018; Van Haren et al., 2013).*

5.2. Pharmacologic agents targeting BBB disruption

Maintaining and/or restoring BBB integrity after TBI is likely important for protection against both VasE and PSH. However, evolutionarily, BBB disruption (and VasE) may be important, indeed necessary, for facilitating the process of neural repair and regeneration. The key to appropriate management may lie in maintaining a delicate balance of enabling neuroprotection/repair while preventing the process from becoming detrimental; the

challenge is in determining where that switch lies and how to control it. While not approved for clinical use, several targeted strategies are being evaluated (Table 2).

5.2.1. ML-7—ML-7 is a MLCK inhibitor that decreases myosin-mediated contraction of endothelial cells, thus decreasing BBB permeability. In preclinical CCI, ML-7 reduced CE and also improved motor and cognitive function (Luh et al., 2010; Rossi et al., 2013). This strategy has not been attempted in humans. Given the ubiquitous distribution of MLCK, there may be substantial side effects, thus necessitating further preclinical studies on dose/timing of administration prior to translation.

5.2.2. Fenofibrate, pioglitazone and rosiglitazone—*Peroxisome proliferator-activated receptor (PPAR) agonists have anti-inflammatory properties, including downregulation of cytokines (TNF, IL-1 β), NF- κ B, expression of ICAM-1 and MMP-9 from PPAR dimerization with retinoid X-receptors (Thal and Neuhaus, 2014; Winkler et al., 2016). Fenofibrate (PPAR- α agonist) stabilized BBB integrity in vitro and decreased BBB permeability and CE in an in vivo FPI model (Besson et al., 2005; Chen et al., 2007; Thal and Neuhaus, 2014). Mechanistically, this has been reported to occur by reducing ICAM-1, iNOS (NOS2), MMP-9, and markers of oxidative stress (e.g., loss of glutathione, glutathione oxidation ratio) (Besson et al., 2005; Chen et al., 2007; Winkler et al., 2016). Pioglitazone and rosiglitazone (PPAR- γ agonists) also have shown promising preliminary results in CCI with reductions in lesion size, proinflammatory cytokine expression and neuronal apoptosis, but have not been evaluated with regards to CE/BBB disruption (Sauerbeck et al., 2011; Yi et al., 2008). One study in CCI suggested that pioglitazone also may have PPAR- γ independent effects, since PPAR- γ inhibition did not reverse its beneficial effect on contusion volume (Thal et al., 2011). Further data are needed to determine the effects of these agents on BBB permeability and outcome in TBI.*

5.2.3. SB-3CT and glibenclamide—MMP-9 inhibition remains an active area of research for reducing BBB disruption. MMP-9 $^{-/-}$ mice have shown improved BBB integrity, decreased vascular permeability, limited ZO-1 degradation, decreased lesion volume, and a controversial effect on outcome after TBI (Muradashvili et al., 2015; Semple et al., 2015a; Wang et al., 2000). SB-3CT is a highly selective inhibitor of MMP-2 and MMP-9. In stroke, SB-3CT reduces laminin degradation and further attenuates BBB damage by reducing occludin loss and claudin-5 redistribution (Cui et al., 2012; Liu et al., 2012). SB-3CT also has shown promising results in preclinical models of TBI (FPI, CCI), with reductions in MMP-9 activity, lesion volume, microglial activation and astrogliosis as well as long term (30-day) protection from cortical and hippocampal damage (Hadass et al., 2013; Jia et al., 2014). There are no current human studies of targeted inhibition in TBI. Glibenclamide, an indirect MMP-9 inhibitor, has shown decreased MMP-9 levels and reduced midline shift in clinical stroke trials (Kimberly et al., 2014; Sheth et al., 2016). While targeted MMP-9 inhibition appears to be a promising avenue for future research, it is also important to emphasize that MMPs, including MMP-9, significantly contribute to neurovascular remodeling and repair, thus rendering the time and degree of MMP-9 modulation critical in determining beneficial versus adverse effects (Chodobski et al., 2011; Zhao et al., 2006).

5.2.4. Vascular endothelial growth inhibitor and Bevacizumab—Vascular endothelial growth inhibitor (VEGI), also known as tumor necrosis factor superfamily-15, is a cytokine that modulates anti-angiogenesis and anti-inflammation, and is balanced with VEGF to maintain homeostasis. In one study of FPI, treatment with exogenous VEGI reduced tissue loss, microgliosis and upregulated tight junction proteins including claudin-5, ZO-1 and occludin, thus protecting the BBB (Gao et al., 2015). However, exogenous VEGF has also been shown to improve neurogenesis and outcome in TBI, while VEGF inhibition can be harmful (Lee and Agoston, 2010; Sköld et al., 2006; Thau-Zuchman et al., 2010). Thus, like many mediators of CE and BBB integrity, there is an important balance between benefit and deleterious effects of shifting homeostasis towards one particular pathway (i.e., VEGI versus VEGF). Timing of modulation may be key: in a human biomarker study (40 subjects, 30 controls), increasing VEGI levels were associated with improved outcomes, whereas VEGF levels were initially associated with adverse effects early post-TBI (days 4–14) but subsequently were associated with recovery (days 14–21); a Day 7 VEGF/VEGI ratio > 2.366 was associated with higher hospital mortality (M. Li et al., 2016).

Bevacizumab, an anti-VEGF antibody with anti-angiogenic effects, has been studied for its beneficial effects on BBB disruption, peri-tumoral edema, and progression-free survival in glioblastoma multiforme (Khasraw et al., 2014). There are no human TBI studies evaluating bevacizumab. One preclinical study of bevacizumab in CCI demonstrated that a single intravenous injection of 10 mg/kg (previously reported to persist for 17±4.7 days in rats), did not influence BBB permeability or water content, but significantly worsened neurologic deficits and contusion volume. While the authors concluded that VEGF expression does not contribute to edema after CCI but may be neuroprotective, it is possible (even likely) that the balance between detrimental versus protective effects is dose- and time-dependent. Further preclinical work is needed to inform potential future human studies of exogenous VEGI or VEGF modulation/activation/inhibition.

5.2.5. Curcumin—Curcumin is an active ingredient of turmeric, and has been found to have anti-inflammatory, anti-carcinogenic, anti-oxidant, and neuroprotective effects in many neurological diseases (W. Li et al., 2016; Qureshi et al., 2018; Reddy et al., 2018; Rodriguez et al., 2016; Yuan et al., 2017; Z.-Y. Zhang et al., 2017). In stroke and subarachnoid hemorrhage, the anti-edema/BBB protective effects of curcumin are proposed to be mediated through various mechanisms including preventing disruption of tight junction proteins (ZO-1, occludin, claudin-5), upregulating glutamate-transporter-1, inhibition of ICAM-1/VCAM-1 and inflammatory cytokines (IL-1 β , IL-6, TNF, NF- κ B), AQP-4 downregulation, reduced MMP-9 expression and inhibition of microglial activation (W. Li et al., 2016; Wang et al., 2013; Yu et al., 2012; Yuan et al., 2017; Z.-Y. Zhang et al., 2017). Preliminary preclinical TBI studies have focused on potential anti-inflammatory and neuroprotective effects (Ashbaugh and McGrew, 2016; Gao et al., 2017, 2016; Samini et al., 2013; Wu et al., 2011; Zhu et al., 2014). One study in CCI found that curcumin significantly reduced brain water content, attenuated IL-1 β and AQP-4 expression, but did not evaluate the BBB; additional studies are needed to further evaluate these findings (Laird et al., 2010).

5.2.6. N-acetyl-L-tryptophan—N-acetyl-L-tryptophan (NAT) is an NK1 tachykinin receptor antagonist with encouraging results in attenuating BBB permeability, CE and functional deficits in TBI (Ameliorate et al., 2017; Donkin et al., 2011, 2009; Gabrielian et al., 2013; Vink et al., 2017). In rodent models, these favorable effects were seen with NAT treatment 30 minutes after TBI, but the therapeutic window extended to 12 hours with evidence of dose dependence (Corrigan et al., 2012; Donkin et al., 2011, 2009). These findings have been replicated in a large-animal (sheep) model of diffuse injury; NAT administration 30 minutes post-injury was associated with a significant and sustained ICP decrease with near-normalization by 4 hours (versus 36% increase in vehicle-treated animals) (Gabrielian et al., 2013). This appears to be a promising therapeutic approach and warrants further investigation.

6. Conclusions

The complexity of CE after TBI is humbling. Over the past few decades, the focus in severe TBI has been on neuronal death, axonal injury and other secondary mechanisms rather than CE. However, a specific focus on CE is emerging as a critical need, given the significant clinical resources dedicated to this condition. This review discusses some known pathophysiologic contributors and targeted treatment prospects, but there are likely many more yet to be discovered. An important step moving forward may be to define quantitative contributions of these various molecular participants in various TBI phenotypes and/or brain regions; a combination of physiological molecular and imaging tools may be essential to such a goal. Current treatments like hypertonic saline, mannitol, or decompressive craniectomy, while effective at reducing intracranial hypertension, have an unclear impact on outcome, highlighting the elusive but essential balance of adaptive versus pathologic swelling. This balance, as well as the underlying mechanisms contributing to CE and clinical ICP targets, may differ between patients based on a variety of characteristics including age, gender, injury characteristics, and genetics. Much like the field of oncology, which has pioneered advances in therapy based on molecular signaling and precision medicine, the future of CE treatment after TBI may require pathophysiology-based targeted treatments. Ongoing discoveries continue to expose exciting new targets, yielding further research in potential therapeutics as well as essential phenotyping of radiographic markers (distinguishing cellular swelling versus BBB disruption), biomarkers (identifying major pathways activated/inhibited) and analysis of multimodal monitoring data (e.g., ICP waveforms, compliance, autoregulation). Although not focused specifically on CE, it is imperative to complement multicenter initiatives such as Transforming Research and Clinical Knowledge in TBI and Collaborative European NeuroTrauma Effectiveness Research in TBI with rigorous preclinical consortiums like Operation Brain Trauma Therapy (Kochanek et al., 2016; Maas et al., 2015; Yue et al., 2013). The tools for implementing a precision-medicine approach to CE after TBI are still in early stages and require significant financial and collaborative support. Nonetheless, the paradigm-shift has begun.

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Abbreviations:

AQP	aquaporin
ASIC	acid sensing ion channel
ATP	adenosine triphosphate
AVP	arginine vasopressin
BBB	blood-brain barrier
CCI	controlled cortical impact
CCL	chemokine (C-C motif) ligand
CNS	central nervous system
CPP	cerebral perfusion pressure
CSF	cerebrospinal fluid
CXCL	chemokine (C-X-C motif) ligand
CytE	cytotoxic edema
EAAT	excitatory amino acid transporter
FPI	fluid percussion injury
Glu	glutamate
H⁺	hydrogen ion
K⁺	potassium ion
HMGB1	high mobility group box-1
ICAM	intracellular adhesion molecule
ICP	intracranial pressure
IL	interleukin
MLCK	myosin light chain kinase
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
Na⁺	sodium ion

NAT	N-acetyl-L-tryptophan
NBC	Na ⁺ /HCO ₃ ⁻ transporter family channel
NF-κB	nuclear factor κB
NHE	Na ⁺ /H ⁺ exchanger
NK	neurokinin
NKCC1	Na ⁺ -K ⁺ -2Cl ⁻ cotransporter
NMDA	N-methyl-D-aspartate
NO	nitric oxide
PMN	polymorphonuclear leukocyte/ neutrophil
PPAR	peroxisome proliferator-activated receptor
PSH	progressive secondary hemorrhage
RCT	randomized controlled trial
SP	substance P
Sur1	sulfonylurea receptor 1
TBI	traumatic brain injury
TGF-β	tumor growth factor β
TLR4	toll like receptor 4
TNF	tumor necrosis factor
Trpm4	transient receptor potential cation channel subfamily M member 4
VasE	vasogenic edema
VCAM	vascular cell adhesion molecule
VEGF	vascular endothelial growth factor
VEGI	vascular endothelial growth inhibitor
ZO	zona occludens

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Highlights

- Brain swelling is a major contributor to adverse outcome in TBI
- Brain swelling in TBI is due to the combined mass effects of extravasated blood, cellular (cytotoxic) edema, vasogenic edema and osmolyte-driven swelling
- Our understanding of molecular mechanisms of edema formation is in its infancy
- Here, we review 12 pathways implicated in edema formation and 11 drugs with potential benefit for targeting edema in TBI

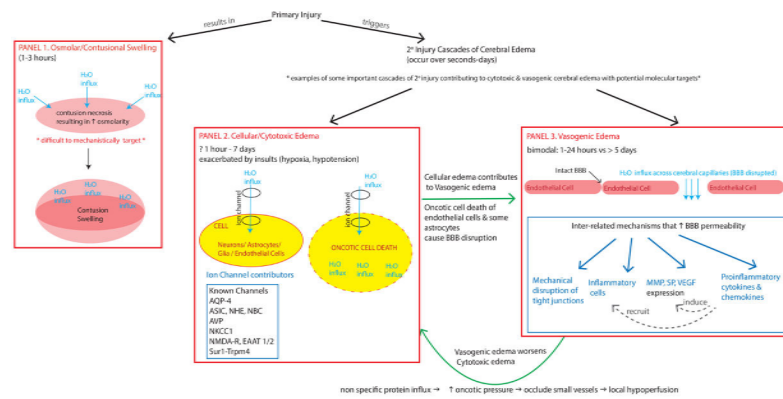


Figure 1. Schema of some key contributors to intracranial swelling after TBI

This diagram highlights different pathways that contribute to intracranial swelling and cerebral edema (CE). Panel 1: Immediately after primary injury, there may be osmolar/contusional swelling. As described by Katayama et al (1992), the necrotic core of the contusion has high osmolarity that drives water movement along this gradient (direction of water movement shown by light blue arrows). This results in acute swelling of the contusion. Primary injury simultaneously triggers many cascades of secondary injury including cellular/cytotoxic edema (CytE, Panel 2) and vasogenic edema (VasE, Panel 3). Some important examples of CytE (Panel 2) include the activation/upregulation of various ion channels (some known channels include AQP4, ASIC, NHE, NBC, AVP, NKCC1, NMDA-R, Sur1-Trpm4). These channels allow water influx into different cell types depending on the cell's expression of the respective channel. Excessive ion-channel related water influx (light blue arrow) into a cell (yellow oval) may result in oncotic cell death. This occurs in neurons/astrocytes/glia and can occur within 1 hour – 7 days. When this process occurs in cells contributing to blood-brain-barrier (BBB) integrity like endothelial cells/some astrocytes, it contributes to VasE (straight green arrow showing relationship between CytE in Panel 2 and VasE in Panel 3). Secondary injury cascades also include additional processes that disrupt the BBB, result in water movement across the disrupted BBB capillaries (light blue arrows) and cause VasE (Panel 3). These cascades include mechanical disruption, release of proinflammatory cytokines and chemokines that recruit migration/activation of inflammatory cells, increased expression and release of factors (such as MMP, SP, VEGF) that disrupt tight junctions and basement membrane proteins. VasE, with its proteinaceous fluid influx, may further raise oncotic pressure in the interstitium, occluding small vessels causing local hypoperfusion, which in turn may further exacerbate CytE development and upregulation of ion channels like Sur1-Trpm4. This relationship is shown by the curved green arrow between Panels 2 & 3).

AQP-4 = aquaporin 4, ASIC = Acid sensing ion channel, NHE = Na^+/H^+ exchanger, NBC = $\text{Na}^+/\text{HCO}_3^-$ transporter family channel, AVP = arginine vasopressin, NKCC1 = $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter, Sur1 = sulfonylurea receptor 1, Trpm4 = transient receptor potential cation channel subfamily M member 4, MMP = matrix metalloproteinase, SP = substance P, VEGF = vascular endothelial growth factor

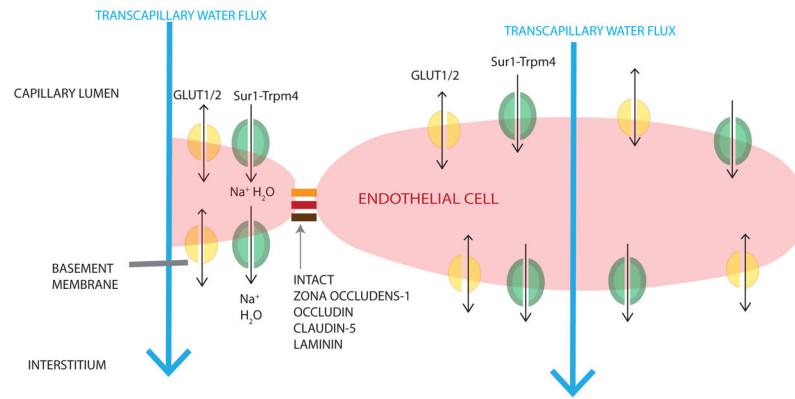


Figure 2. Mechanisms contributing to ionic edema after TBI

The diagram is oriented such that the capillary lumen is superior to the endothelial cell, and the *interstitium and neuronal/glia tissue is inferior*. Ionic edema involves the transcapillary net water flux (large light blue arrow) from the capillary lumen to the brain interstitium without violation of the BBB or basement membrane. Like cellular/cytotoxic edema (CytE), water is transported through luminal ion channels (e.g. GLUT1/2 (shown in yellow), Sur1-Trpm4 (shown in green), NKCC1, NHE1/2, ASIC, NBC, EAAT1/2, SGLT1) into the endothelial cell; water is subsequently transported out of the endothelial cells by channels expressed abluminally (GLUT1/2 (yellow), Sur1-Trpm4 (green)) primarily due to an osmotic gradient created by CytE. Single arrows (black) are used for water co-transport, double headed arrows are used for passive water movement through a channel pore.

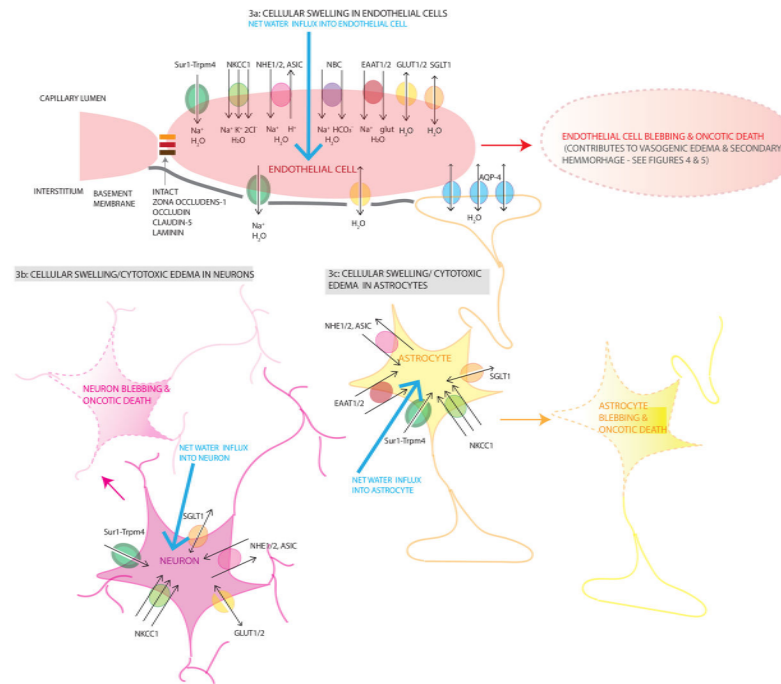


Figure 3. Mechanisms contributing to cellular/cytotoxic edema after TBI

3a Endothelial (light pink cells) cellular swelling results from net water influx (large light blue arrow) into an endothelial cell driven by ionic contributors including GLUT1/2 (yellow channel), Sur1-Trpm4 (green channel), NKCC1 (light green channel), NHE1/2 (pink channel), ASIC (pink channel), NBC (purple channel), EAAT1/2 (red channel), SGLT1 (orange channel)). Sur1-Trpm4 cotransports Na^+ with water into the cell, NKCC1 transports 1 Na^+ , 1 K^+ , 2 Cl^- with 1 molecule of water into the cell, NHE 1/2 transports Na^+ into the cell (with 1 molecule of water) and H^+ out of the cell. NBC transports Na^+ and HCO_3^- into the cell. EAAT1/2 transport 1 Na^+ and 1 glutamate into the cell with 1 molecule of water. GLUT1/2 and SGLT1 transport glucose and Na^+ into the cell respectively with water passively following. At this stage, the tight junctions are intact (solid orange/red/brown links between endothelial cells) as is the basement membrane (solid gray line under the endothelial layer). Cellular swelling/CytE in neurons (dark pink cells, 3b) and astrocytes (yellow cells, 3c) occurs by the same mechanisms with the same ion pumps and channels resulting in Na^+ and water entering the cells causing cellular swelling (large light blue arrows). Eventually, this cellular swelling becomes cytotoxic and causes cell blebbing and oncotoc death illustrated using lightened colors and dashed membrane outlines. Astrocytic endfeet also express AQP-4 at the blood-brain and blood-CSF junctions that allow passive water transport driven by an osmotic or pressure gradient. During cellular swelling, this gradient may direct water inwards. However, during vasogenic edema, these channels may be important in water egress from the cells as shown in Figure 4. Single arrows (black) are used for water co-transport, double headed arrows are used for passive water movement through a channel pore.

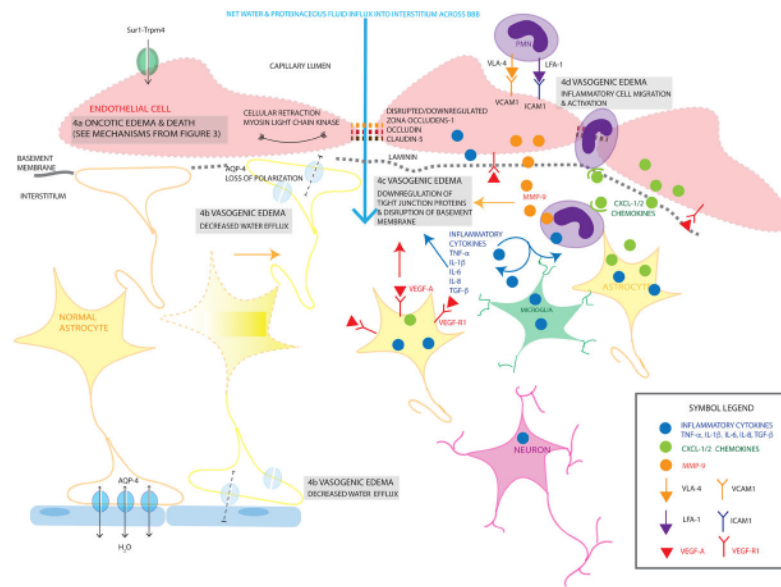


Figure 4. Mechanisms contributing to vasogenic edema after TBI

Vasogenic edema (VasE) results from BBB compromise resulting in net water and proteinaceous fluid influx into the interstitium (large light blue arrow). There are multiple contributors to this process including cellular retraction (via actin and myosin light chain kinase contraction of the cytoskeleton), cytotoxic edema in endothelial cells resulting in membrane disruption and eventual oncotic death (4a), decreased water efflux (4b), degradation of tight junction proteins and disruption of the basement membrane (4c) and activation of inflammatory cells (4d). *Mechanistic details of oncotic edema in endothelial cells (4a) are depicted earlier in Figure 3. Decreased water efflux (4b) also contributes to VasE; one potential mechanism illustrated here is by a loss of polarization of AQP-4 channels in the perivascular and peri-ependymal endfeet (depicted with a faded blue AQP4 channel). Additionally, as astrocytes undergo cell blebbing/oncotic cell death, their endfeet are no longer able to contribute towards sealing the BBB, furthering VasE formation. Another contributor to VasE is due to downregulation of tight junction proteins and disruption of the basement membrane (4c). Tight junction degradation involves proteins such as zona occludens, occludin, laminin shown by the interrupted links (orange/red/brown) between endothelial cells. Disrupted laminin/basement membrane is shown by the dashed-gray line under the endothelial cells. This occurs via multiple proposed mechanisms including MMP-9 (orange filled circles) produced primarily by neutrophils (purple cells) and endothelial cells, inflammatory cytokines (blue filled circles, TNF, IL-1 β , IL-6, IL-8, TGF- β) produced by multiple cell types activated by injury including neurons, microglia, astrocytes, endothelial cells and migrating leukocytes, and VEGF-A (red filled triangle) and VEGF-R1 (red-Y shaped receptor) upregulation by multiple cell types including endothelial cells and astrocytes. Activation of and migration of inflammatory cells further exacerbates VasE (4d). PMNs adhere to the luminal endothelial cell surface via upregulated receptors/ligands such as VCAM-1 (orange Y-shaped receptor) and VLA-4 (orange filled arrowhead), ICAM-1 (purple Y-shaped receptor) and LFA-1 (purple filled arrowhead). Their migration into the interstitium is facilitated by chemokines (CXCL-1/2 for PMNs, green filled circles) secreted by astrocytes and other activated cells, and upregulated chemokine receptors. Each channel/cytokine/cell-type/chemokine/receptor*

is labelled once, and the same color and shape scheme is maintained for each item throughout the diagram with a legend provided in the inset panel. Cell types are labelled and color-coded in the figure: endothelial cells (light red), astrocytes (yellow), neurons (blue), polymorphonuclear leukocytes (PMN, purple), microglia (green). Single arrows (black) are used for water co-transport, double headed arrows are used for passive water movement through a channel pore.

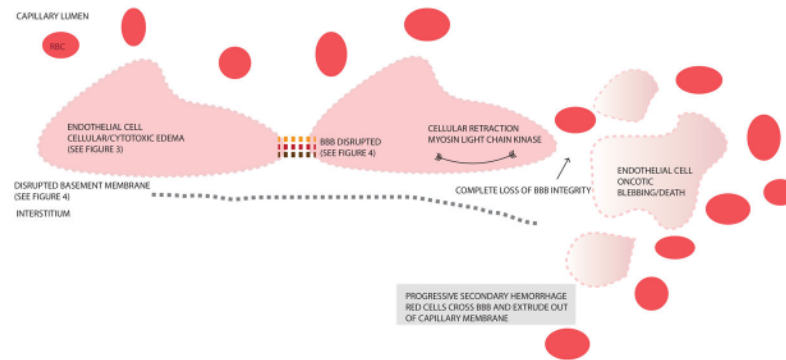


Figure 5. Progressive Secondary Hemorrhage

This figure depicts consequences of blood brain barrier (BBB) breakdown with loss of tight junctions (interrupted orange/red/brown links between endothelial cells), disrupted basement membrane, retraction of endothelial cells, and oncotic cell blebbing/death of endothelial cells. This ultimately destroys all BBB integrity, allowing extravasation of blood components across the capillary membrane eventually resulting in progressive secondary hemorrhage (PSH). Details of the precursor CytE and VasE mechanisms that lead up to these processes and PSH are outlined in Figures 3 and 4.

Table 1:

Pharmacologic agents targeting cellular swelling

<i>Agent</i>	<i>Target</i>	<i>Preclinical TBI models</i>	<i>Human Studies</i>
Bumetanide	NKCC1 inhibitor	<ul style="list-style-type: none"> ● ↓ cellular swelling ● ↓ BBB disruption (? via MMP-9, AQP-4 upregulation) 	NCT00830531 (neonatal seizures)
AER-271	AQP-4 inhibitor	<ul style="list-style-type: none"> ● ↓ ICP in CCI + HS ● No effect on brain water 	-
Aquaporinab	AQP-4 monoclonal antibody	-	-
Glibenclamide	Sur1-Trpm4 inhibitor	<ul style="list-style-type: none"> ● ↓ regional edema ● ↓ ICP ● ↓ PSH ● ↓ BBB disruption ● improve functional outcome 	NCT01454154 (TBI) GAMES-RP (Ischemic stroke, Lancet Neurol, 2016)
Amiloride	NHE-1 ASIC1a	<ul style="list-style-type: none"> ● ↓ brain water (weight drop) 	-
SR 49059	V1a receptor antagonist	<ul style="list-style-type: none"> ● ↓ ICP ● ↓ brain water ● ↓ contusion volume 	-
V1880	V1 receptor antagonist	<ul style="list-style-type: none"> ● ↓ ICP ● ↓ contusion volume 	-

Table 2:

Pharmacologic agents targeting blood brain barrier disruption

<i>Agent</i>	<i>Target</i>	<i>Preclinical TBI models</i>	<i>Human Studies</i>
ML-7	MLCK inhibitor	<ul style="list-style-type: none"> ● ↓ BBB disruption ● Improved motor/cognitive function 	-
Fenofibrate	PPAR- α agonist	<ul style="list-style-type: none"> ● ↓ BBB permeability (FPI) 	-
Pioglitazone/Rosiglitazone	PPAR- γ agonist	<ul style="list-style-type: none"> ● ↓ contusion volume ● ↓ pro-inflammatory cytokine expression ● ↓ neuronal apoptosis 	-
SB-3CT	MMP-2/9 inhibitor	<ul style="list-style-type: none"> ● ↓ BBB disruption ● ↓ lesion volume ● ↓ microglial activation & astrogliosis ● ↓ cortical & hippocampal damage 	-
VEGI	VEGI	<ul style="list-style-type: none"> ● ↓ tissue loss ● ↓ claudin-5, ZO-1, occludin 	-
Bevacizumab	Anti-VEGF antibody	<ul style="list-style-type: none"> ● No effect on ICP/brain water ● Worse functional outcome 	Beneficial in human glioblastoma multiforme
Curcumin	Unk (multiple potential)	<ul style="list-style-type: none"> ● ↓ inflammation ● ↓ brain water content 	
NAT	NK1 receptor antagonist	<ul style="list-style-type: none"> ● ↓ BBB permeability ● ↓ brain water ● ↓ ICP 	