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CURRENT PERSPECTIVES

The Medical Management of Cerebral Edema: Past, Present, and Future Therapies

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Abstract
Cerebral edema is commonly associated with cerebral pathology, and the clinical manifestation is largely related to the underlying lesioned tissue. Brain edema usually amplifies the dysfunction of the lesioned tissue and the burden of cerebral edema correlates with increased morbidity and mortality across diseases. Our modern-day approach to the medical management of cerebral edema has largely revolved around, an increasingly artificial distinction between cytotoxic and vasogenic cerebral edema. These nontargeted interventions such as hyperosmolar agents and sedation have been the mainstay in clinical practice and offer noneloquent solutions to a dire problem. Our current understanding of the underlying molecular mechanisms driving cerebral edema is becoming much more advanced, with differences being identified across diseases and populations. As our understanding of the underlying molecular mechanisms in neuronal injury continues to expand, so too is the list of targeted therapies in the pipeline. Here we present a brief review of the molecular mechanisms driving cerebral edema and a current overview of our understanding of the molecular targets being investigated.

Key Words Cerebral edema · cytotoxic edema · vasogenic edema · hyperosmolar therapy · elevated ICP.

Introduction

Cerebral edema is the pathologic accumulation of intracellular and interstitial brain tissue water [1, 2] that is commonly associated with neurologic pathology. The clinical manifestation is largely related to the primary brain pathology and the associated brain edema usually amplifies the dysfunction of the lesioned tissue. The clinical presentation of cerebral edema varies widely depending on the primary brain pathology from asymptomatic, mild worsening of deficits, coma, and brain death. As a potential complication of both primary neurologic and nonneurologic disorders [1], increased burden of cerebral edema correlates with increased morbidity and mortality across diseases [3–6]. A growing understanding of the cellular mechanisms underlying cerebral edema have re-invigorated the scientific community to identify better targeted therapeutics for the management of cerebral edema [2, 7–9]. The focus of this review will be to discuss the distinct cellular pathways leading to cerebral edema, discuss the current and investigational pharmacologic treatment strategies for management of cerebral edema, and briefly discuss the future therapeutic strategies currently being investigated.

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Pathophysiology of Cerebral Edema

The cellular mechanisms resulting in cerebral edema are divided into three distinct categories: cytotoxic edema, vasogenic edema, and hydrostatic edema [1, 10].

Cytotoxic Edema and Ionic Pump Failure

Cytotoxic edema results from an influx of ions, primarily Na^+ and Cl^-, from the interstitial space into the intracellular compartment, carrying with it water that results in oncotic cellular swelling [7]. The formation of cytotoxic edema has been documented in all central nervous system cell types [7, 11]; however, astrocytes appear to be the most sensitive [12]. Cytotoxic edema does not on its own generate tissue swelling, as it simply leads to the intracellular movement of interstitial water

[11]. However, this disruption of ionic transport across cellular membranes leads to alteration in the primary and secondary drivers of active and secondarily active transport cellular transport [7]; rearrangement of one ion (i.e., Na^+) requires the movement of additional ions (i.e., Cl^-) to maintain electrical and osmotic neutrality. This attempt to maintain homeostasis rapidly becomes maladaptive and leads to cellular swelling and depletion of intracellular adenosine triphosphate (ATP) and it is this maladaptive maintenance of ionic transport that characterizes cytotoxic edema [7, 11].

There are however, a few particularly important cellular targets integral to cytotoxic edema. The constitutively expressed NKCC1 transporter is located primarily on astrocytes and found in all regions of the adult brain [13] and activated in the setting of ischemia, trauma, and acute liver failure [14]. Although molecular regulation of this transporter is complex, there is growing *in vivo* and *in vitro* data suggesting that modulation of this transporter may regulate cytotoxic edema [11, 13, 14]. The pathologic role of the NKCC1 transporter in the injured brain is not the only example of maladaptive transmembrane channels. Aquaporins particularly aquaporin-4 (AQP-4), the major AQP expressed on astrocytes [15], are gaining recognition for their role in cytotoxic edema [16–18]. When ionic transport is abnormal in pathologic states, AQPs facilitate transport of water across the blood–brain barrier (BBB) and therefore worsen cerebral edema in the setting of an intact BBB [17, 18]. Although the precise contribution of AQP physiology to cerebral edema remains unclear, AQP-4 knockout animal models have demonstrated reduced astrocyte swelling under cytotoxic conditions [18]. The last main constitutively expressed membrane transporter that contributed to cytotoxic edema is the sodium–hydrogen antiporter (NHE) family [19]. This luminal family of transporters, the NHE proteins facilitate Na^+ influx across the BBB membranes in hypoxic and hypoglycemic states following ischemia, leading to the development of cytotoxic cerebral edema [19].

Cytotoxic edema is not simply the result of maladaptive normal cellular mechanism. Aberrant cellular transporters additionally form under specific pathologic states. One such transporter, transient receptor potential melastatin 4 (Trpm4), is a naturally existing cation that is activated in the presence of depleted cytosolic ATP [20]. Alone, Trmp4 is activated by intracellular Ca^{2+} [21]. However, in the presence of cerebral pathology such as ischemia, astrocytes exhibit expression of an additional transporter, sulfonylurea receptor 1 (Sur1) [21]. These transports Trpm4 and Sur1 physically associate to form Sur1Trpm4, which has furthermore been implicated in astrocyte and brain edema [22, 23].

Cytotoxic edema additionally results from exposure to endogenous toxins. One such endogenous toxin is glutamate. Following neuronal injury such as ischemia or trauma [24, 25], glutamate accumulates and can lead to neuronal lysis and astrocyte swelling [26]. One potential mechanism for astrocyte swelling could be via the metabotropic glutamate receptor 5 (mGluR5) complex with Na^+/K^+-ATPase and AQP-4 [27]. When mGluR5 is minimally expressed in the normal healthy brain, if glutamate uptake is inhibited in the pathologic brain, neurotoxicity and cytotoxic edema may be worsened [28].

Vasogenic Edema, BBB Disruption, and the Ensuing Inflammatory Response

Vasogenic edema results from edema formation in the absence of an intact BBB [29]. In the absence of an intact BBB, protein and water communicate between the vascular compartment and the interstitial compartment [30]. Contrary to cytotoxic edema, in which ionic forces are the primary driver [7], hydrostatic forces drive the formation of vasogenic edema [31]. During cerebral injury, inflammation and ischemia contribute to endothelial injury and increase permeability [32]. One such mechanism by which BBB permeability is increased in cerebral injury is via increased expression of vascular endothelial growth factor (VEGF) [33, 34].VEGF decouples tight junctions, leading to permeability of cerebral vasculature and increased edema [33]. This is not simply a maladaptive mechanism; however, it is believed to potentially promote angiogenesis to at risk brain in at risk territories [9]. VEGF is not the only molecular signaling that degrades the BBB and contributes to vasogenic edema; matrix metalloproteinase (MMP) activity is increased in territories of cerebral injury [35]. MMP activity however actively degrades the integrity of the microvascular matrix leading to increase edema formation [36].

This destruction of the BBB free communication of the intravascular space with the cerebral interstitial space leads to extravasation of hemorrhage [7]. Local hemorrhage and the degradation of these blood products are quite toxic to the surrounding cells [9, 37, 38]. Once such mechanism is via the secretion of tumor necrosis factor (TNF) and interleukin-1β, Toll receptors, and other inflammatory cytokines that inhibit the BBB's integrity [7, 35, 39]. The ensuing inflammatory response can continue for multiple days and contributes to the formation of reactive oxygen species, MMP activation, and further BBB breakdown [38, 39].

Hydrostatic Edema

Hydrostatic edema is the result of unfavorable hydrostatic pressure vectors between intracranial vasculature, ventricular system, and brain parenchyma [40], leading to transependymal movement of cerebral spinal fluid (CSF) into the brain parenchyma [10]. The mainstay of treatment for this pathology is primarily surgical (CSF diversion, surgical decompression) [10] and is largely outside the scope of this discussion.

Targeted and Nontargeted Therapeutics for Cerebral Edema

Historically, identifying the underlying mechanism of cerebral edema directly influenced the primary treatment of choice. Traditionally, vasogenic edema was treated with agents such as hyperosmolar therapies and corticosteroids, while the efficacy of treatment options for cytotoxic edema remain limited [10]. That being said, the use of nontargeted therapies such as osmolar agents, sedation, neuromuscular blockade, and temperature management have been used in the acute management of cytotoxic edema [1]. Based on a growing understanding of the cellular mechanisms driving cytotoxic and vasogenic edema, a growing list of targeted therapies are in the pipeline for the medical management of cytotoxic and vasogenic edema [8].

Nontargeted Therapies

Nontargeted therapies are the current clinical mainstay for the medical management of cerebral edema. At this point in time, there are five main classes of nontargeted therapies of the management of cerebral edema. These agents have undergone various stages of preclinical and clinical research (see Table 1).

Osmolar therapies

The use of hyperosmolar therapies (e.g., urea, mannitol, hypertonic saline) leverages the selective permeability of an intact blood–brain barrier. The goal of hyperosmolar therapy is to create an osmotic gradient within the cerebral vasculature, where the dominant diffusion vectors are from the parenchyma to the vascular space, thereby decreasing the intracranial free water volume and decreasing intracerebral pressure [42]. This osmotic gradient requires an intact blood–brain barrier, where solute permeability across the BBB depends largely on the agent's reflection coefficient [43]. Of note, there are cellular transport channels and carrier proteins that facilitate movement of these molecules (saline and urea) across the BBB into the parenchyma; however, the greatest component of transport remains intravascularly due to concentration gradients [42]. Therefore, the reflection coefficient of each agent represents the degree to which each molecule is able to diffuse passively across an intact BBB membrane and defines the selectivity of the BBB for this solute [43]. Reflection coefficients, inherent to the molecular properties of each solute, are measured on a 0 to 1 scale, with 0 representing complete permeability and 1 representing complete exclusion to passive movement across a membrane [43]. Those agents that have been identified to be most effective hyperosmolar agents are those whose reflection coefficients approach 1 [44].

Table 1 Mechanism of action, level of evidence, and ongoing clinical trials for nontargeted therapies for cerebral edema

Therapy	Mechanism of Action	Level of evidence*	Ongoing human trials listed at Clinicaltrials.gov†
Osmolar therapies			
Urea	Osmotic gradient	Class III-harm, level C-LD	None
Mannitol		Class IIa, level B-NR	NCT03573999
Hypertonic saline		Class IIa, level B-NR	NCT02798601, NCT03330704, NCT03573999
Diuretics	Optimizing osmotic gradients of osmolar therapies	Class III-harm	None
Anesthesia and sedation			
Propofol	Decreasing cerebral metabolic rate, decreasing cerebral blood flow	Class IIb, level B-NR	None
Barbiturate		Class IIb, level B-NR	None
Hypothermia	Multifactorial	Class IIb, level B-NR	NCT01607151, NCT01886222
Glucocorticoids	Multifactorial	Class IIa, level C-LD	NCT03341676

*Class and level designation is based on the ACC/AHA Task Force Statement Clinical Practice Guideline Recommendation Classification System [41]

† All trials listed at https://clinicaltrials.gov/ as of April 2019. All trials reported are recruiting, active, or completed with official results pending at time of search

Urea The use of hyperosmolar therapies, such as urea, is first described as early as the mid-1950s [45]. The use of hyperosmolar solutions of urea rapidly fell out of favor given the many negative side effects attributed to their infusion. Gastrointestinal disturbances, electrocardiographic complications, coagulopathy, and, perhaps most importantly, rebound cerebral edema, due to the relatively low reflection coefficient of urea (0.59) [46], were only some of the reason's urea fell out of favor [47]. This however allowed for the use of mannitol solutions to take hold in the medical management of cerebral edema.

No randomized clinical trials are available for the use of urea in the management of cerebral edema. Clinical experience has been reported in by Javid et al. in the 1950s [45, 48]. The majority of the physiologic evidence is obtained from animal models [47, 49].

Mannitol First described in the early 1960s [50], mannitol remains part of the routine medical management of cerebral edema. Mannitol is most widely available as a 20% solution and administered on a weight-based bolus dosing schedule: 0.5 to 2 mg/kg [10]. Continuous infusions of mannitol are no longer used clinically, as rebound cerebral edema due to mannitol deposition in the area of compromised cerebral blood–brain barriers are now clearly described [51]. The proposed mechanism of action for mannitol is through direct osmotic effects on astrocytes and neurons with intact blood–brain barriers, as well as opening tight junctions within the blood–brain barrier to enhance osmotic pull of intracellular cerebral fluid into the intravascular space [52]. Mannitol has a reflection coefficient of 0.9 [47] which facilitates its ability to remain intravascular and provide this osmotic pull. Although the osmotic diuresis seen with mannitol does facilitate reduction in cerebral edema, redistribution of the cerebral plasma volume ultimately leads to increased cerebral blood flow and a concomitant vasoconstrictive response of the intracerebral vasculature that decreases intracerebral pressure [53]. Although effective in ICP control, mannitol has potentially adverse unintended consequences [54, 55]. Mannitol initially and fairly rapidly induces increased intravascular volume, which has the potential to precipitate acute hypervolemia intravascularly and lead to acute pulmonary edema or heart failure in patients predisposed to these conditions [55]. After the initial increase in intravascular volume, mannitol exerts its effect as a potent osmotic diuretic; the diuresis which follows mannitol administration can lead to intravascular volume loss, hypotension that may lead to acute kidney injury and worst outcomes particularly in patients with TBI [54, 55]. Clinicians need to be aware of these effects and address them proactively to ensure optimal outcome in patients.

Hypertonic Saline It was not until the 1990s when the use of hypertonic saline fluids gained widespread acceptance as a first-line agent for the management of cerebral edema [56]. Now a mainstay in clinical practice for the management of cerebral edema hypertonic saline fluids are available in varying concentrations based on institutional practices, from 2 to 23.4% [10]. Similar to the mechanism of action of mannitol, hypertonic saline exerts osmotic properties on cerebral tissues with intact blood–brain barriers, drawing intracellular fluid intravascularly to reduce cerebral volume [46]. Due to the higher reflection coefficient of sodium chloride (1.0) [46], it is believed that hypertonic saline may be even more effective than mannitol and have a lower rate of rebound cerebral edema. In contrast to mannitol, hypertonic saline does not cause diuresis and hypovolemia, but instead increases intravascular volume. Complications of hypertonic saline administration include metabolic derangements, volume overload, phlebitis, hypotension (particularly with rapid infusions of high concentrations of hypertonic solutions), and coagulopathy to name a few [57]. Hypertonic saline is administered in bolus of 250 to 500 ml volumes [42], typically in 3% concentrations, or as a salvage technique with 30 ml bolus of 23.4% saline concentrations [58]. Continuous infusions of hypertonic saline are also used to maintain osmotic gradients [59]; however, when doing so, targeted sodium levels should be identified and serum sodium levels should remain below 160 mmol/l [60]. Hypertonic saline has additional, potentially beneficial effects beyond its role in mitigating cerebral edema. Hypertonic saline, when administered, can improve mean arterial pressure, cardiac output, and stroke volume, potentially lifesaving in traumatic injuries or septic shock [55, 61].

Up until this point, there have been small randomized clinical trials demonstrating the beneficial effects of hypertonic saline in the management of cerebral edema; however, the demonstration of improvement in patient outcome had remained elusive. However, recently announced is the COBI trial, continuous hyperosmolar therapy for traumatic brain injured patients' trial, which is a phase 3 clinical trial that has been designed to test whether continuous infusions of hypertonic 20% saline may improve clinical outcomes in moderate to severe traumatic brain injury, with planned completion in February of 2020 (Clinicaltrial.gov; NCT03143751).

Diuretics

Loop diuretics, such as furosemide, have been described and used independently for the management of cerebral edema; however, the results of clinical studies have been inconsistent [62]. Specifically, the administration of diuresis in acute intracranial hypertension and cerebral edema can lead to acute hypovolemia, drop in mean arterial pressure, and potentially worst cerebral perfusion and poor clinical outcomes. Such was seen in a recent trial of administration of furosemide for brain relaxation (Clinicaltrials.gov; NCT01054404). Because of this, the routine use of loop diuretics as a sole management of cerebral edema is not routine clinical practice. There is however data to suggest that furosemide, dosed at 0.7 mg/kg, can prolong the reversal of the blood–brain barrier osmotic gradient established with hypertonic saline and mannitol by primarily excreting free water [62, 63].

Anesthesia and Sedation

Anesthetic agents are part of the medical management of elevated intracerebral pressure. Although not directly affecting cerebral edema, per se, pharmacologically induced coma lowers intracerebral pressure through lowering the cerebral metabolic demand of neurons and thus lowering the intracranial arterial volume [10, 46]. Although there is no clear direct effect on cerebral edema, barbiturates, such as thiopental, phenobarbital, and pentobarbital [46, 64], have long been instituted in the treatment of traumatic brain injury and elevated

intracerebral pressure [65]. The most recent traumatic brain injury guidelines include the use of barbiturate coma to management of refractory elevated intracerebral pressure, however, not as a prophylactic measure [66]. There is no clear evidence supporting the use of barbiturate induced coma in the management of cerebral edema for tumor, intracerebral hemorrhage, or ischemic stroke [46]. Barbiturate induced coma should be used with caution; however, given the lack of demonstrable improvement in clinical outcomes [65], the use of this strategy remains somewhat controversial in the USA [64]. Additionally, many complications from high-dose barbiturate therapy including hypotension, immunosuppression, and hypothermia further limit the benefits from this intervention [46, 65]. When employed pentobarbital is, in general, the agent of choice for treatment given its intermediate half-life of ~20 h. Pentobarbital dosing is typically titrated to sustained intracerebral pressure control or burst suppression on electroencephalogram [46].

Propofol, 2,6-dilsopropylphenol, a sedative used routinely in intensive care units, also is employed in the medical management of elevated intracranial pressure. The Brain Trauma Foundation TBI Guidelines, however, reports caution when using propofol infusion for the management of elevated ICP in TBI patients, as similar to barbiturates, clinically beneficial outcomes with propofol are not clearly established [66]. The hypothesized mechanism of propofol on reduction of intracerebral pressure is via reduction in cerebral metabolic rate and thus reducing cerebral blood volume [60]. There is, however, growing evidence to suggest a more direct effect of propofol on cerebral edema via modulation of aquaporin-4 [67, 68]. This modulation in aquaporin-4 is believed to decreased the subsequent neuroinflammatory response by attenuating the expression of IL-1β and TNF-α expression [68]. Although the exact mechanism of propofol's effects on cerebral edema and intracranial pressure remain unclear, the clinical utilization of propofol for the management of cerebral edema has not been extensively studied in human populations [69]. However, when used in clinical practice, propofol bolus and continuous infusion is considered second line therapy for the medical management of elevated intracerebral pressure by the Neurocritical Care Society [60]. It is important to bear in mind that a subset of patients who are treated with propofol infusions, particularly those of younger ages and treated with higher doses [70], may develop propofol infusion syndrome [71], metabolic acidosis, rhabdomyolysis, cardiac dysfunction, and hypertriglyceridemia which may be fatal [60, 66, 70].

Midazolam, a benzodiazepine; fentanyl, an opiate; and dexmedetomidine, a centrally acting α2 adrenergic receptor agonist, all may be used as adjunctive interventions for the management of elevated cerebral pressures [69]. The mechanism of each is indirect and believed to be through systemic effects on pain management and systemic vascular resistance. These agents are not mainstays in the medical management of cerebral edema.

Hypothermia

Induced hypothermia or targeted temperature management, to 32–35 °C, for the management of elevated intracerebral pressure is well-known [72]. The mechanisms by which hypothermia treats elevated intracerebral pressure and cerebral edema is thought to be multifactorial. Firstly, hypothermia is thought to lower the cerebral metabolic rate and thus limit the risk of sodium pump failure, calcium influx, and cellular death [73]. Hypothermia is additionally thought to attenuate free radical production and pro-inflammatory cytokines and maintain cerebral perfusion which collectively mitigates the formation of cytotoxic edema formation [73–75]. Finally, a direct effect on cerebral vasogenic edema within human clinical studies has additionally been described [76]. Although there are clinical data to suggest a mechanistic effect on cerebral edema and elevated intracranial pressure, one of the most recent clinical trials does not suggest improved clinical outcomes with induced hypothermia plus standard management in TBI patients with elevated intracerebral pressure [77].

Glucocorticoids

Glucocorticoids have been the clinical mainstay for management of perilesional vasogenic edema [78]. The mechanisms through which glucocorticoids act on vasogenic edema are many. Glucocorticoids bind to the glucocorticoid receptor releasing heat-shock proteins and translocating to the nucleus mediating transcriptional changes [79]. Some transcriptional mediators are upregulated, such as glucocorticoid-induced leucine zipper [80] that are responsible for the transcription of proteins that suppress inflammatory mediators such as AP-1 and NF-κB [81]. There are additional direct interactions between glucocorticoid bound, glucocorticoid receptor homodimer and AP-1 and NF-κB, which result in decreased pro-inflammatory cytokine release and direct reduction in peritumoral vasogenic cerebral edema [82]. Although these are the postulated primary mechanisms for glucocorticoids on vasogenic cerebral edema, many preclinical studies suggest that they may mediate many additional pathways including VEGF, multiple aquaporin pathways, multiple claudin pathways, and via MMP/TIMP mechanisms [78]. Although many of these targets appear to be important in *in vivo* models, the specific pathways mediating vasogenic edema in brain neoplasms in humans remains less clear.

Glucocorticoids are not recommended for the management of cytotoxic cerebral edema in traumatic brain injury, intracerebral hemorrhage, or stroke [66, 83, 84], although the role of glucocorticoids in aneurysmal subarachnoid hemorrhage remains unclear [85].

Potential Targeted Therapies

Our approach to the medical management of cerebral edema has largely revolved around an increasingly artificial distinction between cytotoxic and vasogenic cerebral edema [7, 35, 86]. A recent and growing understanding of the molecular mechanisms underlying cerebral edema in neurologic injury has provided a framework within which to identify novel therapeutic targets and potential promise for new clinical interventions [87]. These potential molecular targets have been identified based on a growing understanding of the cell–cell signaling that occurs amongst the neurovascular unit [88–90]. The neurovascular unit is the conceptual paradigm describing the cellular signaling that occurs between glial, vascular, and neuronal partitions within the central nervous system (CNS) [90]. The dynamic interplay of cellular signals within the neurovascular unit is not only important for trophic support but also increasingly recognized as active during and after CNS injury, releasing neurotoxic inflammatory mediators, coordinating cellular remodeling, and organizing recovery [89, 90]. The role of these molecular signals in the clinical management of cerebral edema remains unclear; many serve as investigational therapeutic targets. However, this review hopes to detail the current landscape of these promising therapeutic interventions (see Table 2).

Bumetanide: a Potential NKCCl Target

Bumetanide is a loop diuretic approved for the management of fluid retention in the management of chronic heart failure [91]. A specific antagonist of the NKCCl transporter [92], bumetanide offers promise for management of cerebral edema through the potential inhibition of this transporter and reduced swelling of astrocytes after injury [13, 14]. Under normal environment conditions and the presence of ATP, NKCCl cotransports ions and water volume to maintain plasma membrane homeostasis [13, 14, 93]. Sodium is transported into endothelial cells and expelled into the interstitial via a sodium potassium ATPase [93]. However, under pathologic stress resulting from ischemia, the blood–brain barrier becomes permeable to an increased concentration of sodium and potassium resulting in increased astrocyte uptake leading to edema [94]. Furthermore, *in vitro* evidence suggests cerebral tissues express increased concentrations of NKCCl [94] and that under conditions of hypoxia, NKCCl appears to be upregulated, further facilitating transport of sodium, potassium, and water interstitially potentiating cerebral edema [95]. There is additional evidence that although NKCCl may play a direct effect on cerebral edema formation, there are perhaps downstream inflammatory effects such as IL-1 that may potentiate cerebral injury [96]. Collectively, this has made bumetanide a potential pharmacologic target for the management of cerebral edema. Animal studies have demonstrated that in the management of cerebral edema in diabetic ketoacidosis [97], ischemic stroke [94], and traumatic brain injury [96, 98] that bumetanide offers promise in lowering the degree of edema seen. Additionally, in the management of perihematomal edema in intracerebral hemorrhage, there is the suggestion that early administration of bumetanide may attenuate perihematomal edema in rats, but may not improve outcomes [92]. There are no reports of bumetanide in the management of cerebral edema in humans.

AER-270, AER-271, and Curcumin: Targeting Aquaporins

Aquaporins are ubiquitous within the human body; however, two main isoforms are primarily prevalent in the central nervous systems of mammals: aquaporin-1 and aquaporin-4 [99]. Within the brain, aquaporin-4 is the most abundant [100] and are localized primarily to the astrocyte foot processes [99, 101]. Aquaporin-4 transporter, although molecularly connected with other neuroinflammatory mediators [87], facilitates intracellular water movement in cytotoxic edema [102] and decreased water clearance from astrocyte foot processes in cytotoxic edema [103, 104]. Given that aquaporin-4 does not appear to have one universal role, the facilitation of water movement, understanding the temporal relationship of aquaporin-4 with cerebral injury, appears paramount. In murine models of traumatic brain injury, there are conflicting reports of the role and regulation of aquaporin-4 within the first 48 h after injury [105, 106]. These observations may however be a manifestation generalized aquaporin dysregulation seen after traumatic brain injury, as seen in an aquaporin knockout mouse model [107] and potentially serve as a compensatory mechanism to counteract cytotoxic edema in favor of vasogenic edema [108]. However, available animal model evidence suggests that in general, aquaporin deletion, or by extension inhibition, may worsen vasogenic edema and limit cytotoxic edema [99, 100, 109].

Although human data is limited, the role of aquaporin-4 upregulation has been reported in traumatic brain injury [110], intracranial neoplasms [111], cerebral infarction [112], and subarachnoid hemorrhage [113], with the degree of upregulation correlating to the degree of cerebral edema [111, 114]. As such, inhibition of aquaporin-4 offers potential promise in the management of cerebral edema. AER-270 and AER-271 (a phosphorylated pro-drug of AER-270) are potentially theraputic small molecules [115]. Demonstrating promise in the management of cerebral edema in animal models [115, 116], the selective aquaporin-4 inhibitor, AER-271, is currently under investigation in phase 1 clinical trial for eventual use in humans for the treatment of acute ischemic stroke (ClinicalTrials.gov Identifier: NCT03804476).[1]

Curcumin, a derivative curry spice rhizome *Curcuma longa* is known for its anti-inflammatory effects and a potent

[1] Phase 1 study to assess AER-271. Clinical Trials.Gov. https://clinicaltrials.gov/ct2/show/NCT03804476 Accessed 3/16/2019

Table 2 Molecular target, level of evidence, and ongoing clinical trials for targeted therapies for cerebral edema

Therapy	Molecular target	Level of evidence*,†	Ongoing human trials listed at Clinicaltrials.gov‡
Bumetanide	NKCCL transporter	Level 5-mechanistic based; no human trials	None
AER-270, AER-271, and curcumin	Aquaporin-4	Level 5-mechanistic based; no human trials	AER-271: NCT03804476
Glibenclamide	Sur1-Trpm4 nonselective cation channel and matrix metalloproteinases	Class IIb, level B-R†; GAMES-RP Trial	NCT03284463 NCT03741530 NCT02864953 NCT02460874
SB-3CT	Matrix metalloproteinases	Level 5-mechanistic based; no human trials	None
Amiloride, SM-20220, and HOE-642	Sodium–hydrogen exchange proteins	Level 5-mechanistic based; no human trials	None
SR 49059, V1880, conivaptan, vasopressin	V1a receptors	Level 5-mechanistic based; no human trials	Conivaptan: NCT03000283
ML-7	Myosin light chain kinase inhibition	Level 5-mechanistic based; no human trials	None
Vascular endothelial growth inhibitor and bevacizumab	Vascular endothelial growth inhibitor and anti-vascular endothelial growth factor antibody	Level 5-mechanistic based; no human trails	Bevacizumab: NCT02819479-completed, results pending; NCT03623347-completed, results pending
NK1 receptor antagonists	Neurokinin-1 (NK1) receptor antagonists	Level 5-mechanistic based; no human trials	None
Fenofibrate, pioglitazone, rosiglitazone	Peroxisome proliferator-activated receptors (PPAR) agonists	Level 5-mechanistic based; no completed human trials	NCT00827892-completed, results pending
HMGB1	Toll receptors	Level 5-mechanistic based; no human trials	None
Fingolimod, RPC1073, RP101075	Sphingomyelin-1-phosphate receptors	Level 5-mechanistic based; no human trials	None

*Level of evidence designation, levels 1 thru 5, is based on the Oxford Centre for Evidence Based Medicine 2011 Levels of Evidence. OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

† Class and level designation is based on the ACC/AHA Task Force Statement Clinical Practice Guideline Recommendation Classification System [41]

‡ All trials listed at https://clinicaltrials.gov/ as of April 2019. All trials reported are recruiting, active, or completed with official results pending at time of search

inhibitor of NF-κB [117]. It has more recently been demonstrated to have additionally anti-inflammatory effects through reduction of IL-1β, which has been demonstrated to directly correlate with aquaporin-4 expression [118]. It therefore is postulated that through reduction in aquaporin-4, curcumin may attenuate cerebral edema [119]. This hypothesis has been supported by growing evidence within rodent models of TBI [117], ischemic stroke [120], hemorrhagic stroke [121], diffuse cerebral hypoxia [119], and cerebral neoplasms [122].

Glibenclamide: Targeting Sur1-Trpm4

Sulfonylurea receptor 1 (Sur1) is a cation channel that is upregulated along capillary beds, astrocytes, and neurons after neurotrauma or ischemia [123]. Once Sur1 is upregulated in the setting of cerebral injury, transient receptor potential melastatin 4 (Trpm4) [124] associates forming a nonselective cation channel ultimately leading to intracellular water influx, edema, and cellular death [123, 124]. With Sur1-Trmp4 not present under normal homeostatic pressure [87], this protein channel offers a promising target for therapeutic development. Sur1 in domains that bind sulfonylurea drugs such as glibenclamide or glyburide, which inhibit the channel activity [124]. Animal models in TBI and hemorrhagic shock have demonstrated promising results in improved functional outcomes and decreased volume of edema [125–127]. This has provided the enthusiasm with which human studies have been pursued. Two small human trials, both in TBI, have demonstrated that with administration of glyburide, decreased contusion expansion rates and improvement in short-term functional outcomes were observed [128, 129]. The culmination of these data largely leads to the creation of a prospective randomized controlled trial investigating the efficacy of glyburide IV administration in the management of large territory ischemic infarcts: GAMES-RP [130]. GAMES-RP recently reported results suggesting improvement in midline shift, levels of alertness, NIH stroke scale scores, and decreased mortality in patients treated with glyburide [131].

This work has largely been the reason glyburide appears to be a very promising intervention in the management of cerebral edema.

Glibenclamide and SB-3CT: Targeting Matrix Metalloproteinases

Glibenclamide is additionally an indirect matrix metalloproteinase (MMP) inhibitor, specifically of MMP-9, which further contributes to its potential as a therapeutic target [130, 131]. There is also growing evidence that MMP-9 plays an important role in stroke recovery, with tissue remodeling, angiogenesis, and neuronal plasticity [132]. The mechanism through which MMP contributes to cerebral edema is via proteolytic cleavage of the basement membrane and disruption of the blood–brain barrier [133]. In cerebral injury MMP is upregulated and thereby reduced the integrity of the underlying BBB, contributing to cerebral edema [133]. Clinically, this has been demonstrated in murine models, in which MMP knockout mice have improved functional outcomes and decreased cerebral edema in traumatic brain injury [134], hepatic encephalopathy [135], ischemic stroke [132], and subarachnoid hemorrhage [136]. SB-3CT, a selective inhibitor of MMP, has been investigated in multiple preclinical models of cerebral injury and has demonstrated promise as a potential translatable target [137–140]. Yet given the ubiquitous nature of MMPs and the prior failed trials utilizing MMP inhibitors for cancer, secondary to undesired side effects should encourage discretion with translation to clinical populations [138]. There is however, an ongoing large clinical trial investigating the use of glibenclamide injection for the management of severe cerebral edema post large hemispheric infarct (ClinicalTrials.gov Identifier: NCT02864953),[2] with results pending.

Amiloride, SM-20220, and HOE-642: Targeting NHE1 and NHE2

Multiple sodium–hydrogen exchange (NHE) protein isoforms exist in humans [19, 141]; however, two isoforms, NHE1 and NHE2, appear to have a particularly important role in the permeability of blood–brain barrier in acute ischemic stroke [19]. NHE1 and NHE2 are both present on luminal blood–brain barrier, stimulated by hypoxia and hypoglycemia, both conditions present in the setting of acute ischemia [142, 143]. Murine model suggests that with small molecule NHE inhibitors, such as SM-20220 and HOE-642, perilesional edema secondary to ischemia can be limited [142, 143]. Amiloride, a thiazide diuretic [144], has additionally been described to decrease cerebral edema via decreased brain water content; however, this precise mechanism has not been completely elucidated [145]. No human studies have been completed to verify these results in clinical populations [2].

SR 49059, V1880, Conivaptan, and Vasopressin: Targeting V1a Receptors

Arginine vasopressin is a nanopeptide that is produced in the hypothalamus and released into the blood stream via the neurohypophysis and is heavily responsible for cerebral water homeostasis [146]. Furthermore, there is growing evidence that arginine vasopressin expression may be related to aquaporin expression in the brain as well [147]. Specifically, V1a receptors facilitate aquaporin-4-mediated water flow in the rat cortices [148]. This observation coupled with results from animal studies identifying V1a as a potential therapeutic target to mediate cerebral edema post TBI and ischemia [148–150] has made small molecules inhibitors of V1a, such as SR 49059 and V1880, of particular interest [2]. Mice models of ischemic and hemorrhagic stroke have demonstrated decreased cerebral edema and improved functional outcomes with pretreatment of SR 49059 [151, 152]. TBI mouse models demonstrate that treatment with V1880 decreases cerebral edema observed post injury [153]. Similar results in reducing cerebral edema have been seen with the mixed V1a and V2a inhibitor, conivaptan, when administered to mice post ischemic stroke [154, 155]. Collectively, these data have supported the development of a single center phase 1 trial of conivaptan for the treatment of intracerebral hemorrhage (ClinicalTrials.gov Identifier: NCT03000283).[3] Vasopressin, an arginine vasopressin agonist, has not demonstrated the expected increase in cerebral edema when administered to patients with TBI [156], calling into question the exact mechanism through which V1a antagonism decreases cerebral edema.

ML-7: Targeting MLCK inhibition

Myosin light chain kinase has been demonstrated to increase cerebral edema [157]. The proposed mechanism via which myosin light chain kinase augments cerebral edema is via contraction of endothelial cells thereby increasing the permeability of the endothelial blood–brain barrier [157, 158]. ML-7 is a small molecule inhibitor of myosin light chain kinase and in preclinical animal studies have demonstrated decreased rates of edema and improved functional outcomes in TBI models [157, 158]. ML-7 has not been translated to human studies as of yet. Endothelial myosin light chain kinase is

[2] Phase 3 study to evaluate the efficacy and safety of intravenous BIIB093 (glibenclamide) for severe cerebral edema following large hemispheric infarction (CHARM). Clinical Trials.gov. https://clinicaltrials.gov/ct2/show/NCT02864953. Accessed 3/18/2019

[3] Conivaptan for the reduction of cerebral edema in intracerebral hemorrhage—a safety and tolerability study. Clinical Trials.Gov. https://clinicaltrials.gov/ct2/show/study/NCT03000283. Accessed 3/16/2019

ubiquitous throughout human endothelial layers, potentially inhibiting the translatability of this target into clinical practice [159].

Vascular Endothelial Growth Inhibitor and Bevacizumab: Targeting Vascular Endothelial Growth Inhibitor and Anti-vascular Endothelial Growth Factor Antibody

Vascular endothelial growth factor (VEGF) is most well-recognized for its role in angiogenesis and vascular homeostasis in the human brain [160, 161]. However, over the past several years, many additional angiogenic independent functions of VEGF have been identified and are likely the reason VEGF expression in the adult brain tends to localize in geographically specific regions in the cerebral tissues [160]. VEGF's role in BBB permeability is clearly delineated, and furthermore, VEGF has been demonstrated to be upregulated in neuronal injury and inducible by hypoxia-inducible factor 1 and hypoxia-inducible factor 2 [161–164]. Once hypoxia-inducible factors are released, MMPs then facilitate cleavage of the native basement membrane, resulting in increased permeability of the native vessel and facilitate extravasation of intraluminal components into the extracellular space [164] The role of VEGF and more specifically VEGF inhibition is best described and most widely used in the management of cerebral neoplasms [165]. One commonly used inhibitor is bevacizumab, a humanized monoclonal antibody against VEGF [166], has demonstrated efficacious effects in the treatment of neoplasms, particularly when combined with chemotherapeutic regiments; with one phase II trial further demonstrated decreased cerebral edema in the treatment arm [167]. Rebound cerebral edema has also been described in patient being treated with bevacizumab for CNS neoplasms who undergo rapid cessation of their treatment [166].

The role of VEGF and VEGF inhibition outside the management of CNS neoplasms is unclear. Within the management of ischemic stroke, it appears that VEGF inhibition reduces the edema formation and decreases the risk of ischemia related reperfusion injury [168]. Although VEGF upregulation may offer some neuroprotective effects, the corresponding increase risk of CNS microbleeds and worsening edema suggests the role VEGF serves for edema regulation may be more important in ischemic injury [169]. TBI models suggest that post traumatic injury, regional upregulation of VEGF is seen [33] and that these regional differences contribute to the formation of post TBI cerebral edema [170]. The importance of VEGF in mediating cerebral edema in TBI has been demonstrated in rats with VEGF receptor antagonism [171]. The role of VEGF upregulation in ischemia and trauma remains unclear in humans. Although we do know that TBI augments VEGF expression in the CSF of humans [172], no human trials have been completed.

NK1 Receptor Antagonists: Targeting NK1

Neurokinin-1 (NK1) receptor antagonists, such as tachykinin receptor antagonist *N*-acetyl-L-tryptophan [173], have been demonstrated to inhibit substance P [174–176]. One of many neuropeptides released in neuronal injury, substance P [177] has been implicated for its role in breaking down the blood–brain barrier leading to increased permeability and the development of cerebral edema [174, 178]. This coupled with the evidence from both animal and human studies that substance P levels in the cortex are elevated in the setting of TBI [178] and ischemia [179, 180]and have made substance P antagonists promising targets for the medical management of cerebral edema. One downstream inhibitor of substance P was the NK1 receptor antagonist SR140333, which demonstrated reduction in infarct volume size in animal models [181]. Additional models in rodents for cerebral and spinal ischemia have replicated these findings with molecular inhibition of NK1 [176, 180]. Similar findings in animal models of TBI have demonstrated similarly promising findings: decreased cerebral edema and improved functional outcomes [174, 175]. Although the efficacy of substance P inhibition has yet to be replicated in human populations, serum substance P levels have been associated with TBI severity and mortality in humans as well [182].

Fenofibrate, Pioglitazone, and Rosiglitazone: Targeting PPAR Agonist

Fenofibrate, pioglitazone, and rosiglitazone are commonly used peroxisome proliferator-activated receptors (PPAR) agonists in clinical practice [183]. PPARs, membrane associated transcription factors, are present in three different isotypes and are all present in the brain [184]. Through a combination of downstream effects, agonism of these PPAR receptors leads to down-transcription of pro-inflammatory mediators [185]. This has led to the application of clinically available PPAR agonists to the management of cerebral edema and neuronal injury. In TBI, fenofibrate [186], pioglitazone [187], and rosiglitazone [188] have demonstrated decreased neuronal inflammation and subsequent decreases in edema when administered in rodent models. Similarly, the PPAR agonists have demonstrated promise in the management of neuronal injury post ischemic stroke models [189–191]. This has led to the development of novel, neuronally designed PPAR agonists, GW0742, for the management of acute stroke, with similarly promising results [192]. Interestingly, PPAR has additionally been demonstrated to be a potential target in the management of cerebral edema post neurosurgical interventions [193], a novel population in which targeted therapy could be very beneficial. Although these findings have also not been translated into human studies, the proposed role of PPAR in neuroinflammation and cerebral edema in intracerebral hemorrhage [194, 195] has

led to the design and completion of a phase 2 clinical trial which has recently been completed (ClinicalTrials.gov Identifier: NCT00827892)[4]; results of which are still pending.

HMGB1: Targeting Toll Receptors

High mobility group box protein 1 (HMGB1) is a DNA binding protein that translocate to the extracellular space following cerebral injury and activates Toll-like receptors [196]. These Toll-like receptors are then responsible for cell signaling which is prompts a secondary neuroinflammatory cascade seen in TBI and ischemic stroke [197]. There appears to be a dose–response relationship between neuronal injury, cerebral edema, and HMGB1 as well in animal models, further making HMGB1 a potential therapeutic target [197]. HMGB1 a-Box, a molecular fragment which competitively inhibits HMGB1 at its receptor binding site, has demonstrated efficacy at reversing edema and improving neurologic function in TBI models [198]. Similar results with small molecule inhibitors or antibodies to HMGB1 have demonstrated promise in the management of intracerebral hemorrhage [199] and subarachnoid hemorrhage [200] models as well. However, when translating these results to human populations, HMGB1 inhibition, either through small molecules or antibodies, has been rife with complications [201]. However probenecid, initially developed to be administered with penicillin and increase serum levels [202], has recently demonstrated efficacious effects at inhibiting HMGB1 levels and decreasing infarct volume size in animals [203]. Given its relatively safe pharmacokinetic profile, it offers a potential early translatable target for clinical populations.

Fingolimod, RPC1063, and RP101075: Targeting Sphingosine-1-Phosphate Receptors

Fingolimod is an established oral medication for the management of multiple sclerosis and targets sphingosine-1-phosphate receptors (S1PR) [9, 204]. Preclinical rodent models have demonstrated improved clinical outcomes of intracerebral hemorrhage by mitigating post injury inflammatory response by inhibiting migration of lymphocytes to the site of injury [9]. Cerebral edema is reduced by lymphocyte suppression and decreased expression of secondary inflammatory cytokines that are believed to exacerbate edema progression [204–206]. S1PRs have multiple subunits, with fingolimod primarily mediating inflammation via S1PR1 binding, although having affinity for additional subunits as in S1PR3 [204]. The importance of S1PR1 selectivity in the mediation of cerebral edema has been tested with the use of RPC1063, a selective S1PR1 modulator, and its active metabolite RP101075 [204, 206]. This active metabolite, RP101075, has been shown to limit cerebral edema in rodent models of intracerebral hemorrhage, enhance BBB integrity, and improve the microvasculature circulation post injury, further suggesting the importance of S1PR1 modulation in cerebral injury [204, 206]. There are no active human clinical trials investigating the effects of S1PR1 on cerebral edema, however, given the promising preclinical models, making sphingomyelin-1-phosphate receptor modulators potentially viable for the management of cerebral edema.

Conclusions and Future Directions

Despite the rapid modernization and development of specialized neurocritical care units and staffed by a subspecialty trained population of neurointensivists and staff [207–209], the medical management of cerebral edema developed within this clinical practice is independent of targeting the underlying cellular and molecular mechanisms that drive it [7]. As a result, the nontargeted therapies that are employed in-practice remain the standard of clinical practice [60] and focus on the downstream effects of cerebral edema formation without modulation of the neuroinflammatory cascade that is paramount in all neuronal injury [29, 210, 211]. However, in the recent years, a growing understanding in the molecular mechanisms of cerebral inflammation, blood–brain barrier permeability, and cerebral edema in all modalities of neuronal injury have led to an inspiring number of potential therapeutic targets [7]. The complicated nature of these pathways is just now becoming clear through animal models in TBI, ischemic stroke, subarachnoid hemorrhage, and cerebral neoplasm. And although a lack of the detailed understanding of many of these pathways have limited the clinical utility targeting many of these molecular targets in clinical practice, our growing understanding of these mechanisms will surely aid in further clinical development of future therapeutics. Few large-scale human trials have been designed around these targeted interventions; however, those that have been completed demonstrated promising results [130, 131]. With several human trials in development (Clinical Trials Identifier: NCT03000283 and NCT03804476), and more on the way, it is clear that our future understanding of targeted medical management of cerebral edema will rapidly evolve, offering promise for a currently pressing clinical problem.

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[4] Safety of Pioglitazone for Hematoma Resolution In Intracerebral Hemorrhage (SHRINC). Clinical Trials.gov. https://clinicaltrials.gov/ct2/show/NCT00827892. Accessed 3/17/2019

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