New drugs on the horizon for cerebral edema: what's in the clinical development pipeline?

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Abstract (< 100 words, per instructions)

Recent research has advanced our understanding of the molecular and cellular mechanisms of cerebral edema ("brain swelling"). This has led, in turn, to the development of novel anti-edema therapeutics. Current evidence supports aberrant neuro-glial ion transport as a central mechanism that underlies pathological fluid accumulation after central nervous system (CNS) injury. Novel agents in the clinical development pipeline are showing promise in altering the natural history and treatment of cerebral edema. In this review, we discuss these agents that are under active investigation, their mechanism, and clinical application in clinical trials.

Body (1000-2000 words, per instructions)

1. Introduction

Cerebral edema, the pathological accumulation of fluid in the brain parenchyma, is caused by multiple traumatic and pathological insults, including traumatic brain injury (TBI), stroke (both hemorrhagic and ischemic), infection, primary and metastatic tumors, and inflammatory disease. Even some systemic diseases, including acute liver failure and diabetic ketoacidosis, can lead to brain swelling. Regardless of the inciting event, a common consequence of cerebral edema is the elevation of intracranial pressure (ICP). Swelling brain tissue and increasing ICPs result in compromised cerebral blood flow, ischemia, cell death, and neurological deficits.[1] Although the severity, location, and extent of swelling determine the specific downstream consequences, the side effects are often severe, frequently affecting patient's functional outcome and increasing mortality to upwards of 80%.[1]

2. Management of Cerebral Edema

The Monro-Kellie doctrine first described by Dr. Alexander Monro and Dr. George Kellie more than two centuries ago, is a well-accepted principle in neurological disease. This principle states that the sum of the volumes of intracerebral blood, cerebrospinal fluid, and brain tissue, consisting of interstitial and intracellular fluid, is constant given the constraints of a rigid skull.[2] An increase

in one must cause a reciprocal decrease in the others. Therefore, current management of cerebral edema focuses on temporizing tissue swelling and decreasing ICPs in effort to prevent brain herniation and ischemia due to effects of high pressures and loss of cerebral blood flow.

Osmotherapy, a common first line management, consists of intravenous administration of hypertonic solution (i.e. mannitol or hypertonic saline). Following Starling's principle, creating an osmotic gradient across blood vessels causes water to move from the intra- and extra-cellular compartments of the brain into the vasculature, decreasing parenchymal fluid volume. This movement of water along an imposed ionic gradient serves to decrease intracranial volume, and as a result, pressures. In addition to osmotherapy, decadron, a glucocorticoid, is commonly used, especially in the setting of tumor-induced edema.[3] Other less commonly used medications for edema include loop diuretics (i.e. furosemide), anti-inflammatory agents, and barbiturates.

Although often first line, medical management is largely temporizing and exposes patients to significant side effects during administration, as well as rebound swelling when therapy is discontinued. Surgical management with decompressive craniectomy is often required if medical therapy fails, or as initial management if the edema is too extensive and urgent intervention is needed. Interestingly, these strategies to reduce cerebral swelling and increasing ICP have been used for over a century.

3. Pathophysiology of Cerebral Edema

Cerebral edema is traditionally classified as cytotoxic or vasogenic, based on location of fluid accumulation. Vasogenic edema causes increased extracellular fluid due to blood-brain barrier (BBB) breakdown, while cytotoxic edema occurs when water accumulates in the intracellular space, resulting in cell swelling. Ionic cerebral edema, more recently defined as a subset of cytotoxic edema, consists of vessel leakage into the extracellular space through an intact BBB.

While historical classifications remain useful, current research is advancing our understanding of the mechanisms underlying cerebral edema. Water balance intracranially is based on intra- and extra-cellular and vascular ionic gradients, which are primarily dictated by cellular transporters and channels. Therefore, current theories ascribe the pathophysiology of cerebral edema to alterations in intracranial ion transport, and new pharmacological targets are being investigated.

4. Antiedema Drugs in Development

As our understanding of the pathophysiology of this disease grows, pharmacological treatments are being developed to target specific molecular mechanisms underlying cerebral edema. New candidates are showing promise attenuating tissue swelling and improving functional outcomes in *in vivo* models and clinical trials. Table 1 illustrates these novel therapeutic agents currently under development.

4.1 Cation-Chloride Cotransporter (CCC) Regulation

Intracranial ionic homeostasis is, in part, maintained by cation-Cl- cotransporters (CCC), specifically NKCC1 and the KCCs. Through phosphorylation, SPS1-related proline/alanine-rich (SPAK) kinase is a master regulator of both, stimulating NKCC1 and inhibiting KCC. As electroneutral cotransporters, NKCC1 imports and KCC1-4 export Cl^- by utilizing the transmembrane gradients of Na^+ and/or K^+. Their coordinated regulation is required for appropriate cellular response and volume changes and prevents pathological cell volume changes in response to alterations in osmotic gradients. SPAK, in combination with OSR1

(oxidative stress-responsive kinase 1), ensures control over cellular Cl⁻ concentrations, and as a result, water movement and cell volume. In experimental models, enhanced SPAK activity has been found in ischemia-induced cerebral edema.

A newly developed selective SPAK inhibitor, ZT-1a (5-chloro-N-(5-chloro-4-((4-chlorophenyl)(cyano)methyl)-2-methylphenyl)-2-hydroxybenzamide), is a modulator of both NKCC1 and KCC, inhibiting and activating these cotransporters, respectively. SPAK inhibition with ZT-1a stimulates Cl⁻ -dependent K⁺ export, and improved regulation of cellular volume after insult. In animal models, ZT-1a reduces ischemia-induced CCC phosphorylation, and results in decreased cerebral edema and improved functional outcomes.[4] Given the specificity of this agent and the promising *in vivo* results, ZT-1a has significant therapeutic potential for cerebral edema.

4.2 SUR1-TRMP4 Inhibition

The sulfonylurea receptor 1 (Sur1) is an ion channel important in cerebral ion homeostasis. Sur1 association with transient receptor potential melastatin 4 (Trpm4) creates SUR1-TRPM4, a non-selective cation channel upregulated in neurons, astrocytes, microglia, oligodendrocytes, and microvascular endothelial cells after cerebral ischemia. SUR1-TRPM4 generates a complex with AQP4, increasing the influx of cations and water into cells, particularly astrocytes. In addition, SUR1 expression contributes to vascular damage that may play a role in vasogenic edema.[3] Glyburide, a second-generation sulfonylurea developed for type 2 diabetes mellitus, targets SUR1-TRPM4 channels and inhibits its upregulation after central nervous system (CNS) injury. *In vivo* work shows glyburide-mediated inhibition after ischemic injury reduces brain swelling and death.[5] With the conclusion of phase 2 clinical trials, evidence supports administration of intravenous glyburide; the greatest benefit was observed in stroke patients with large hemispheric infarcts, with a reduction in parenchymal swelling and improved functional outcomes and mortality (ClinicalTrials.gov Identifiers: NCT01268683; NCT01794182). Given this success, a phase 3 clinical trial is currently underway (ClinicalTrials.gov Identifiers: NCT02864953).

4.3 Vascular Endothelial Growth Factor (VEGF) Inhibition

Intracranial malignancies, both primary and metastatic, cause significant peri-lesional edema. While the development of tumor-mediated edema is more chronic, it can be difficult to manage and often causes significant morbidity and mortality. Vascular endothelial growth factor (VEGF), a glycoprotein upregulated in intracranial malignancies, contributes to tumor angiogenesis and formation of interendothelial gaps, fragmentations, and fenestrations in the brain endothelium. Bevacizumab, a monoclonal immunoglobulin G humanized antibody against VEGF-A, and Cerdiranib, a VEGFR tyrosine kinase antagonist, have emerged as promising anti-angiogenic and anti-edema therapies.[6,7] Although VEGF inhibition by these drugs does not improve overall patient survival, animal studies and clinical trials demonstrate normalization of tumor vasculature, reduction in the severity of peritumoral edema, and improvement of progression-free survival in both animal studies and clinical trials (ClinicalTrials.gov NCT00943826; NCT00305656).

4.4 Arginine Vasopressin (AVP) Receptor Inhibition

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), a peptide produced in the posterior pituitary, has been indicated in intracerebral volume regulation. AVP exerts homeostatic effects via signaling through G protein-coupled receptors expressed on vasculature (V$_{1A}$), the anterior pituitary gland (V$_{1B}$/V$_3$), and components of the nephron tubule (V$_2$), allowing control of body fluid volume. Present in non-pathological CSF, AVP demonstrates an ability to increase brain water content,[1] and plasma concentrations have been found to be significantly

increased in stroke patients.[8] Furthermore, hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is present in a significant number of TBI and SAH patients and indirectly causes worsening brain edema.

Vaptans, small-molecule vasopressin receptor inhibitors, are showing modest effect on controlling cerebral edema. Administration of the AVP A_{1A}/A_2 receptor inhibitor, conivaptan, demonstrated reduction of brain edema in a rodent model, and is now being investigated in an ongoing phase 1 clinical trial (ClinicalTrials.gov Identifier: NCT03000283). However, while the effects of conivaptan on water retention in the kidney have been well characterized, little is known regarding the pharmaceutical's mechanism of action in the brain, warranting further molecular research.

4.5 Inflammatory Cascade Inhibition

Proinflammatory cascades induced by CNS injury often contribute to widespread cerebral edema in patients. Cyclooxygenase (COX) enzymes convert arachidonic acid into proinflammatory mediators, which play a key pathological role in amplifying injuries, especially in the setting of intracerebral hemorrhage (ICH). In rodent models of ICH, COX2 is upregulated in endothelium and leukocytes, exacerbating the progression of neuronal cell death, infarct volume, and brain edema.[1,9] In a retrospective study, ICH patients treated with celecoxib, a non-steroidal inhibitor of COX2, demonstrated attenuated hematoma expansion and decreased edema.[1] A 2009 pilot clinical trial of 44 patients demonstrated similar findings, showing reduced hematoma expansion and perihematomal edema in patients treated with celecoxib versus standard management (ClinicalTrials.gov Identifier: NCT00526214). Celecoxib treatment following cerebral hemorrhage failed to show sustained improvements in functional outcomes, however, further work is being done and more specific COX inhibitors are being developed and investigated.[10]

Signaling through sphingosine-1-phosphate (S1P) and its receptors S1P1-5 stimulates propagation of inflammatory responses. Expressed by all cell types in the CNS, S1P receptors are upregulated in neuroinflammatory conditions such as stroke. Each receptor type demonstrates a unique function determined by its location of expression. S1P1, S1P2, and S1P3, expressed on neuro-endothelial cells, regulate vascular and BBB permeability. Given the prominent role S1P2 plays in disrupting intercellular adherens junctions and increasing vascular permeability, it is of particular interest as a potential therapeutic target in brain edema. Fingolimod, a S1P receptor modulator, originally approved to treat multiple sclerosis, is being repurposed for treatment of brain edema, with promising preliminary and clinical data. In rodent models of ICH, fingolimod mitigated the onset and progression of cerebral edema.[11] In a phase 2 clinical trial of patients with either ischemic or hemorrhagic stroke, fingolimod reduced perihematomal edema and lesional growth, and improved neurological outcomes (ClinicalTrials.gov Identifier: NCT02002390). Given the multiple roles of S1P, however, the mechanism by which fingolimod exerts its effect remains elusive, necessitating further research. Development of a specific S1P2 inhibitor may allow direct inhibition of vasogenic edema, mitigating off-target effects.

4.6 Corticotrophin-Releasing Factor Therapy

Although corticosteroid therapy has proven effective for management of cerebral edema, the significant systemic side effect profile has prompted development of "steroid-sparing" therapies. Of these, human corticotrophin-releasing factor (hCRF) has as shown promise clinically. Alternatively named Xerecept, this synthetic, modified hypothalamic peptide demonstrates protective effects on brain endothelium and a lower incidence of the severe side effects associated with corticosteroid treatment when given systemically. Administration of Xerecept in a RG2 cell-derived glioma rodent model significantly reduces vasogenic brain edema[12] and a

completed phase I clinical trial demonstrated improved neurological outcomes and reduced peritumoral edema in 10 of 17 primary brain tumor patients.[13] A follow up phase 3 clinical trial of 200 brain tumor patients showed that Xerecept was effective in reducing steroid requirements and steroid-related side effects such as myopathy and Cushing's Syndrome (ClinicalTrials.gov Identifier: NCT00088166).

5. Conclusion

Cerebral edema is a significant contributor to the morbidity and mortality of many central nervous system pathologies, especially with acute injuries and disease. Current treatment options are limited, and standard of care management include temporizing intracranial pressures with the administration of hypertonic solutions, corticosteroids, and in the most severe cases, craniectomy. However, as our understanding of the molecular drivers of cerebral edema improves, several new therapeutic agents are being developed and tested in animal models and clinical trials with promising results. With new and specific pharmacological targets to effectively treat, and even prevent, brain swelling, patients may be spared the significant consequences and brain damage associated with elevated ICPs and cerebral ischemia.

6. Expert Opinion

As an underlying theme in most neurologic and neurosurgical diseases, cerebral edema represents a common secondary pathology leading to increased mortality and neurological deficits in patients. Clinical management of edema largely centers on temporizing strategies to minimize consequences of acute fluid accumulation, specifically mass effect and elevated ICPs. Corticosteroids are used for longer term management; however, their side effect profile often limits their utility and chronic administration.

Fortunately, our understanding of the molecular and cellular mechanisms underlying the pathophysiology of cerebral edema is growing significantly, allowing the development of targeted antiedema agents. The most promising candidates are those targeting the specific molecular mechanisms controlling the compensatory post-injury response of ion channels and transporters leading to the pathological alteration of osmotic gradients. Although further clinical studies are needed, repurposing of drugs such as glyburide to inhibit the aberrant upregulation of ion channels like SUR1-TRPM4, and newly developed agents such as ZT-1a which re-establish physiological regulation of ion channels like NKCC1/KCC, appear to restore ion gradient homeostasis to prevent and reverse fluid accumulation in the brain parenchyma.

Although cerebral edema across all CNS pathologies has a likely common underlying pathophysiology, it is important to consider the unique characteristics of these lesion separately. TBI, an acute and global CNS injury, likely involves different molecular drivers than peritumoral edema or perilesional edema in hemorrhagic or ischemic stroke territories. Similarly, timing of drug administration is also a consideration. Injuries such as TBI and ICH stimulate acute production of pro-edema environment, such as the upregulation of SUR1-TRPM4 channels and enhancement of SPAK activity peri-lesionally. However, in chronic and evolving oncological lesions, upregulation of VEGF pathway and inflammatory cascades through both aberrant CNS signaling, as well as pathological signaling from the tumor itself, offer alternative pathways for drug targets. Repurposing current drugs will be beneficial in shortening the translational timeline between *in vivo* research and clinical application, and agents such as COX2 inhibitors and VEGF inhibitor bevacizumab offer critical avenues for expansion of antiedema agents available clinically.

In vivo and clinical trials are gaining momentum and, although there remain hurdles to overcome in developing effective and novel therapeutics for cerebral edema, promising targets are being identified, driving new pharmaceutical development. As we answer important questions regarding the molecular drivers of cerebral edema and treatment strategies, clinical management of cerebral edema will become more targeted and effective.

Table 1: Summary of novel therapeutics with promising preclinical and clinical findings in brain edema

Drug	Target	Experimental Investigation	Preclinical Findings	Clinical Trials	Clinical Trial Patient Population	Clinical Trial Results
ZT-1a	SPAK	Zhang et al. 2020[4]	ZT-1a reduced NKCC1 and KCC3 phosphorylation, mitigating cerebral edema and improving functional outcomes in a rat model of stroke	N/A	N/A	N/A
Glyburide	SUR1-TRPM4	Simard et al. 2006[5]	Glyburide attenuated brain water volume and decreased 7-day mortality from 65% to 24% in a rat model of middle cerebral artery occlusion	NCT01268683; Phase 2a; Completed in 2013	10 patients with a 82-210 mL acute MCA or MCA/ACA ischemic stroke	Improved clinical outcomes and attenuated vasogenic edema
				NCT01794182; Phase 2; Completed in 2016	83 patients with a 82-300 mL acute MCA ischemic stroke	Attenuated NIH stroke scale scores and reduced 30-day mortality rates, however, the primary and secondary outcome goals were not met
				NCT02864953; Phase 3; Ongoing	Aims to recruit 680 patients with 80-300 mL acute MCA ischemic stroke	N/A
Bevacizumab	VEGF-A	Folkins et al. 2007[6]	Bevacizumab reduced BBB permeability and normalized tumoral and peritumoral vasculature	No identifier; Phase 2; Completed in 2007	32 patients with progressive or recurrent grade III/IV gliomas who were treated with radiation and not surgical intervention	Reduced tumor size and edema resulting in improved neurological outcomes
				NCT00943826; Phase 3; Completed in 2015	921 patients with stable or decreasing glucocorticoid use and a newly diagnosed, untreated glioblastoma	Improved length of progression-free survival and maintenance of baseline performance, but failed to improve overall survival
Cerdiranib	VEGFR	Kamoun et al. 2009[14]	Cerdiranib reduced tumor vasculature permeability and size, as well as expansion of edema	NCT00305656; Phase 2; Completed in 2012	31 patients with a confirmed diagnosis of glioblastoma	More typical vascular development around the tumor and mitigated development of cerebral edema
Celecoxib	COX2	Chu et al. 2004[9]	Celecoxib treatment in rats with induced cerebral hemorrhage reduced edema, inflammation, and cell death, leading to increased functional recovery	NCT00526214; Pilot Trial; Completed in 2009	44 patients with diagnosed intracerebral hemorrhage not caused by trauma, aneurysmal bleeding, or anticoagulation	Mitigated hematoma and perihematomal edema progression and expansion
Fingolimod	S1P Receptors	Wei et al. 2011[11]	Fingolimod reduced infarct volume, neuronal cell death, edema, and neurological dysfunction in a mouse model of middle cerebral artery occlusion	NCT02002390; Phase 2; Completed in 2014	22 patients with ischemic stroke or intracerebral hemorrhage not caused by coagulopathy, trauma, or thrombocytopenia	Reduced edema and improved neurological outcomes in hemorrhage patients and reduced lesional expansion and improved neurological functioning in stroke patients
Conivaptan	AVP A_{1A}/A_2	Can et al. 2019[15]	Conivaptan was shown to be a more potent diuretic than mannitol in a rat model of ischemic brain injury	NCT03000283; Pilot Trial; Ongoing	Goal of 7 patients with an intracerebral hemorrhage of >20 mL not due to thrombolysis, infection, trauma, or tumor	N/A
Xerecept	Unknown	Tjuvajev et al. 1996[12]	Xerecept directly acted on tumor microvasculature, reducing permeability and vasogenic edema in rats with RG2 cell-derived gliomas	No identifier; Phase 1; Completed in 1998	17 patients with primary brain tumors and radiographic evidence of edema	10 of 17 patients in the clinical trial had improved neurological outcomes
				NCT00088166; Phase 3; Completed in 2008	200 patients with a brain tumor and complications from prior steroid use	Reduced steroid requirements and steroid-associated side effects such as Cushing's Syndrome and myopathy

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