Brain Edema is an excess accumulation of water in the intracellular and/or extracellular spaces of the brain. It may be due to traumatic brain injury, neoplasm, infection, or following surgery. Advent of electron microscope and molecular pathophysiology of fluid transport through blood–brain barrier has elucidated the mechanism of edema formation, that is, ion channels and transport of fluid into extracellular space. Currently approved treatments, such as decompressive craniectomy and osmotherapy, controlled hyperventilation, and administration of diuretics, were developed prior to any knowledge of modern cerebral edema pathophysiology. These therapies attempt to manage downstream end-stage events without directly attenuating the underlying molecular mechanisms of cerebral edema. Next few years will yield new knowledge of how particular proteins drive edema influx, paving the way for rationally designed therapeutics that directly target key steps in cerebral edema formation, thereby achieving what currently approved therapies do not. Pharmacological agents which can block edema formation are being tried experimentally and clinically. Development in imaging, that is, computed tomography and diffusion tensor magnetic resonance imaging, has helped in antemortem assessment of evolution and resolution of brain edema as a dynamic pathophysiology. Animal studies show release of vasoactive substances, that is, histamine, serotonin, adrenaline, nitric oxide, substance P, prostaglandins, tumor necrosis factor-α, and cytokines, in the injured brain results in activation of inflammatory cascade, which is the important cause of brain edema.
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Escapees into extracellular space, for example, infarction and neurotoxic agents. Ionic edema, an extracellular edema that occurs in the presence of an intact BBB, forms immediately following cytotoxic edema.

Osmotic edema occurs when plasma dilution decreases serum osmolality, resulting in a higher osmolality in the brain compared with the serum. This creates an abnormal pressure gradient and movement of water into the brain, which can cause progressive cerebral edema, resulting in a spectrum of signs and symptoms from headache and ataxia to seizures and coma, for example, water intoxication and hepatic failure.

Hydrocephalic edema (intracellular) occurs in obstructive hydrocephalus due to a rupture of the cerebrospinal fluid (CSF)–brain barrier. This results in transepidermal flow of CSF, causing CSF to penetrate the brain and spread to the extracellular spaces and the white matter. Interstitial cerebral edema differs from vasogenic edema as CSF contains almost no protein.

Experimental/Clinical Studies

Since the release of vasoactive chemicals in the injured tissue of live human being is difficult to demonstrate, we used animal head injury models by direct demonstration of vasoactive substances done in the injured brain. Samples of edematous brain were collected during surgery, and blood samples of head injured patients were collected serially demonstrating rise of vasoactive substances. Prognosis following head injury patients correlated well with the decrease and normalization of vasoactive agents. Interestingly, immunological studies in severely head injured patients shows rebuilt of antibrain antibodies possibly due to escape of cerebroproteins to circulation.

Inflammatory substances mediating vasogenic brain edema has been studied in rats, dogs, rabbits, and cats. Trauma was produced by stab wound of the brain in the former and fall of weight in the later animals. Intracerebral hemorrhage was created by injecting blood into the brain of rats. Important finding was the release of vasoactive substances resulting in inflammation, that is, histamine, serotonin, adrenaline, nitric oxide, substance P, prostaglandins, tumor necrosis factor-α, and cytokines, in the injured brain. Recent studies reveal important role of inflammation as a cause of edema formation. All those substances play an important role in opening the endothelial junction and efflux of fluid, leukocytes, and platelet into the extracellular space. They also help in the escape of intravascular fluid through endothelial cells by pinocytosis. Increased levels of biogenic amines and tissue enzymes in the blood/CSF is an indirect evidence of increased BBB permeability and related to prognosis.

Pathogenesis

Disruption of the BBB is the most important prerequisite for edema formation. Several mediators have been discovered to act at the BBB either passively or actively. Serum which escapes into the extracellular spaces ultimately increase tissue volume and raise intracranial pressure (ICP). Both vasogenic and cytotoxic edema results in increased ICP and eventually decreased cerebral perfusion pressure (CPP). This is in line with the Monro–Kellie hypothesis which states that “the sum of the intracranial volumes of blood, brain, CSF, and other components is constant and that an increase in any one of these must be offset by an equal decrease in another.” Elevated ICP and diminished cerebral perfusion can lead to tissue ischemia. Ischemia in turn activates autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilation increases cerebral blood volume, which in turn increases ICP, lower CPP, and provokes further ischemia.

After traumatic brain injury, cerebral blood flow (CBF) autoregulation is impaired or abolished in most patients. When pressure autoregulation is impaired or absent, ICP decreases and increases with change in CPP. Also, autoregulatory vasoconstriction seems to be more resistant compared with autoregulatory vasodilation which indicated that patients are more sensitive to damage from low rather than high CPPs. Molecular biologic studies recently reveals trance endothelial passage of fluid into the extracellular space resulting in brain edema by active transporter and aquaporins.

Treatment of Brain Edema

The goal of medical management of cerebral edema is to maintain optimal ICP, ensure regional and global CBF to meet the metabolic requirements of the brain, and prevent secondary neuronal injury from cerebral ischemia.

Standard medical management of cerebral edema involves using a systemic approach, from general measures, that is, optimal head and neck positioning for facilitating intracranial venous outflow, proper airway, avoidance of dehydration, and systemic hypotension, and maintenance of normothermia, to specific therapeutic interventions like controlled hyperventilation, administration of diuretics, osmotherapy, and pharmacological cerebral metabolic suppression. Some of the drugs clinically used and others under experimental studies are listed in Table 1.

Future treatment is possibility of drug cocktail which will be useful to prevent secondary brain injury and protect the neurons.
**Table 1** Drugs reducing vasogenic brain edema

<table>
<thead>
<tr>
<th>Factors increasing edema</th>
<th>Inhibitory/Blocking substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion channel cotransporter-Na⁺-K⁺-2Cl⁻ co运输器 suri regulator NC C8-ATP</td>
<td>Bumetanide, Glibenclamide</td>
</tr>
<tr>
<td>• Vasopressin (V1 A and V2 receptor) antagonist</td>
<td>Conivaptan</td>
</tr>
<tr>
<td>• Inflammation mediators</td>
<td>Anti-inflammatory drugs, i.e., indomethacin, steroids, Pentoxifylline, pCPA, H₂-blockers-ranitidine/cimetidine, Ibuprofen</td>
</tr>
<tr>
<td>• Oxidative mediators</td>
<td>Cortisone, CRF</td>
</tr>
<tr>
<td>• Adhesion mediators</td>
<td>Metamizol, Acetzolamide</td>
</tr>
<tr>
<td>• Cytokines, IL-1α, 1β, TNFα, IL-6</td>
<td>Dextran, Urea</td>
</tr>
<tr>
<td>• Chemokines</td>
<td>SC236 and dexamethasone rofecoxib</td>
</tr>
<tr>
<td>• Catecholamines</td>
<td>Iron chelation</td>
</tr>
<tr>
<td>• Enzymes (increases blood and CSF)</td>
<td>Indomethacin, Cyclosporin A, Cicitoline lactate, NMDA receptor antagonists–fenprodil, Scavengers–vitamin C and E 21 aminosteroids, Edaravone, N-acetyl cysteine, Citicholine, Endothelin antagonists–patent EPO 838223 CL transport inhibitor–torase, CA inhibitors–acetazolamide agonist, niravoline, dexamethasone, and HCRF</td>
</tr>
<tr>
<td>• Hemoglobin degradation product (free iron)</td>
<td>Endogenous inhibitors (long chain fatty acids)</td>
</tr>
<tr>
<td>• Free fatty acids</td>
<td>Endogenous inhibitors (long chain fatty acids)</td>
</tr>
<tr>
<td>• Prostaglandins mitochondrial permeability damage cerebral anaerobic metabolism polyamines free radicals endothelin chloride transport carbonic anhydrase kappa opioid aquaporin 4</td>
<td>Endogenous inhibitors (long chain fatty acids)</td>
</tr>
</tbody>
</table>

Abbreviations: CA, carbonic anhydrase; CL, chloride; CRF, corticotropin-releasing factor; HCRF, human corticotropin-releasing factor; IL, interleukin; TNF, tumor necrosis factor.

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**Fig. 1** Resolution of traumatic edema (A–C). (A) Postinjury, (B) 72 hours later (20% mannitol intravenously 100 mL/8 hours), (C) 2 weeks later (no intravenous mannitol).

**Fig. 2** (A–C) Resolution of peritumoral edema (diffusion tensor magnetic resonance imaging [DT-MRI]) with dexamethasone treatment. (A) Before steroid therapy, (B) 24 hours after steroid therapy, (C) 72 hours after steroid therapy.

**Conclusion**

Currently approved treatments for cerebral edema—decompressive craniectomy and osmotherapy—were developed prior to any knowledge of modern cerebral edema pathophysiology. These therapies attempt to manage downstream end-stage events without directly attenuating the underlying molecular mechanisms of cerebral edema.

The water movements involved in cerebral edema are dependent upon ionic fluxes, which are ultimately mediated by individual channels and transporters. The study of cerebral edema is essentially the study of maladaptive ion transport. While significant gaps still remain in our understanding of how specific proteins contribute to cerebral edema, the fields of cerebral edema and brain CSF dynamics are robust and productive. Doubtlessly, the next few years will yield new knowledge of how particular proteins drive edema transport, inflammatory mediators released from endothelium, platelets, and glial cells.

**Surgical decompression** and use of osmotherapy to reduce brain edema and its deleterious effect remains the mainstay of treatment even today. This only attenuates the primary injury but cannot abate the secondary cascade of events. Drugs which inhibit or slow the various secondary mechanisms are still in an experimental stage.
influx, paving the way for rationally designed therapeutics that directly target key steps in cerebral edema formation, thereby achieving what currently approved therapies do not.

Conflict of Interest
None declared.

References