A review of progress in understanding the pathophysiology and treatment of brain edema

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Object. Brain edema resulting from traumatic brain injury (TBI) or ischemia if uncontrolled exhausts volume reserve and leads to raised intracranial pressure and brain herniation. The basic types of edema—vasogenic and cytotoxic—were classified 50 years ago, and their definitions remain intact.

Methods. In this paper the author provides a review of progress over the past several decades in understanding the pathophysiology of the edematous process and the success and failures of treatment. Recent progress focused on those manuscripts that were published within the past 5 years.

Results. Perhaps the most exciting new findings that speak to both the control of production and resolution of edema in both trauma and ischemia are the recent studies that have focused on the newly described “water channels” or aquaporins. Other important findings relate to the predominance of cellular edema in TBI.

Conclusions. Significant new findings have been made in understanding the pathophysiology of brain edema; however, less progress has been made in treatment. Aquaporin water channels offer hope for modulating and abating the devastating effects of fulminating brain edema in trauma and stroke.

KEY WORDS • brain edema • ischemic edema • traumatic edema • vasogenic edema

THE CONTRIBUTION OF brain edema to brain swelling in cases of traumatic injury, ischemia, and tumor remains a critical problem for which there is currently no effective clinical treatment. It is also well documented that in head injury, swelling leads to elevations in ICP, which is a frequent cause of death, and to poor prognosis among survivors.^{44,100,112,151,152} A poor prognosis is certain when secondary insults of hypotension or hypoxia are added to the mechanical injury.³¹ In the case of TBI, the swelling process has been classified into four distinct degrees of severity based on studies in the Traumatic Coma Data Bank.^{106–108} Of great importance is the fact that the degree of swelling assessed on the first computed tomography scan, obtained soon after injury, was highly correlated with outcome ($p < 0.0002$),⁴⁰ and it suggests that therapy must be commenced as soon as possible to avoid neurological deterioration or even death. The rise in ICP may be swift, and brain herniation and death can occur within 36 hours postinjury despite aggressive therapy of mannitol, vasopressors, hyperventilation, and barbiturates. The reason for this may be explained by the exponential relationship between ICP and brain water content.

As edema develops, a threshold is reached in which ICP rises exponentially to small changes in brain edema.¹⁰⁵

This clearly emphasizes the need for a better understanding of the processes leading to brain swelling, and most important, the means by which these processes can be abated. In this manuscript I review the most recent concepts and advances in the pathobiology of brain edema and the implications for treatment.

Types of Edema and Implications for Treatment

By definition, edema is an abnormal accumulation of fluid within the brain parenchyma; it is subdivided into vasogenic and cytotoxic types.⁸⁴ Other labels of edema such as osmotic, interstitial (hydrostatic), or hyperemic refer to etiology rather than physical location.¹⁷⁶ Vasogenic edema is defined as fluid originating from blood vessels that accumulates around cells. Cytotoxic edema is defined as fluid accumulating within cells as a result of injury. The most common cytotoxic edema occurs in cerebral ischemia. Heretofore, the edema specific to TBI has generally been considered to be of vasogenic origin, secondary to traumatic opening of the BBB.^{15–17} However, both forms of edema can coexist. This is a critical problem, as effective treatment will clearly depend on the major type of edema contributing to the swelling process.

In the case of vasogenic edema, protein extravasation

Abbreviations used in this paper: ADC = apparent diffusion coefficient; APQ = aquaporin; BBB = blood–brain barrier; CBF = cerebral blood flow; CSF = cerebrospinal fluid; ICP = intracranial pressure; MR = magnetic resonance; TBI = traumatic brain injury.

secondary to barrier compromise was implicated in the edematous process.⁹¹ This was in line with Klatzos' theory that a breakdown of the extracellular proteins would increase the osmotic gradient and cause more water to exude from the vessels. It was shown that protein in the extracellular space retards the clearance of fluid,⁵² but no evidence to date has been put forth to substantiate that extracellular protein increases fluid entry into brain. Just as protein in the extracellular space has been shown to retard clearance, lowering the ICP enhances clearance of fluid from the brain, while steroids have negligible effect on the clearance process.⁶⁸ Mediator compounds such as bradykinin, glutamate, arachidonic acid, and leukotrienes are released upon brain injury and cause brain swelling.^{13, 14, 36, 47, 59, 61, 80, 81, 96, 125, 146, 150, 161, 164, 167, 174, 175} Pharmacological treatments in the laboratory setting have shown positive effects to varying degrees,^{47, 50, 61, 76, 81, 114, 125, 167} however, these treatments have not been translated to the patient. Moreover, mannitol, which is in common use after stroke, has not been shown to be effective, despite a plethora of nonrandomized in-hospital trials.¹⁸

The Importance of Cellular Edema

The treatment of cellular edema is far more complex, given that a precise identification of the processes that govern resolution as well as entry of fluid into the cell is unknown. Cellular brain edema is a life-threatening complication of cerebral infarction.¹⁴⁷ The molecular cascade initiated by cerebral ischemia includes the loss of membrane ionic pumps and cell swelling. Secondary formation of free radicals and proteases disrupts brain cell membranes, causing irreversible damage. New diagnostic methods based on MR imaging have markedly improved diagnostic accuracy. Cytotoxic and vasogenic edema are greatest by 24 to 72 hours after the ischemic event. Thrombolytics reperfuse tissue and improve outcome; when treatment is delayed, they can increase edema and BBB opening. Although osmotherapy reduces brain water and is used to treat ischemic edema, its efficacy remains to be proven. With regard to trauma, the use of experimental models of head injury in earlier work has shown that drugs inhibiting K^+ -stimulated HCO_3^- -dependent swelling of brain cerebrocortical slices were effective in inhibiting astrocytic swelling. Qualitative and quantitative electron microscope studies have shown that members of the fluorenyl class of drugs inhibit astrocytic swelling associated with an experimental animal head injury model. It was posited that astrocytic swelling in pathological states may be partly due to activation of Cl^-/HCO_3^- and Na^+/H^+ exchange systems driven by increased astrocytic intracellular hydration of CO_2 .

Cellular Edema in Ischemia

Results of both experimental and clinical studies have indicated that cerebral edema develops following acute regional ischemia and can cause mass effect and herniation that results in a further decrease in CBF. Complete interruption of CBF, as induced in cardiac arrest, results in the rapid breakdown of all electrophysiological and metabolic functions of the brain.⁶³ The edema associated with

ischemia has a characteristic time course and begins with a cytotoxic phase in which energy failure results in intracellular fluid accumulation associated with shifts in sodium and potassium between intra- and extracellular compartments of the brain.^{10, 20–22, 29, 30, 35, 38, 41, 45, 51, 57, 67, 72–74, 79, 88, 90, 92, 111, 126, 131, 142, 145, 148, 154, 155, 179, 191, 195} With ongoing ischemia, the core region of impaired metabolism expands, leading to gradual infarction of the penumbra.⁶² Treatments for the combination of ischemic edema and eventual vasogenic edema secondary to barrier compromise have not been successful, and more work needs to be done, not only to elucidate the pathophysiology but to better understand the process of cellular edema resolution.^{2, 24, 48, 53–56, 60, 64, 81, 97, 115, 133, 138–141, 165, 182, 187, 194}

Edema Development Following Intracerebral Hemorrhage

The vasogenic and cellular components of edema following trauma and/or ischemia are well described. However, the cause of the edema development following intracerebral hemorrhage remains unknown. Studies involving stereotactic injection of various blood products such as concentrated blood cells, serum from clotted blood, and plasma from unclotted blood all failed to produce experimental edema in rodents. However, the introduction of prothrombinase to plasma to activate the coagulation cascade produced brain edema.⁹⁹ Authors of subsequent studies have demonstrated that thrombin increased brain edema when concentrations as low as 1 U/ μ l were infused into rodent brain.⁹⁸ Work is ongoing to develop strategies for combating initiation of the coagulation cascade.^{113, 130, 190, 197}

Cellular Edema in TBI

Results of recent studies of TBI have indicated that the predominant type of edema in these injuries is cellular.⁶⁶ These results have been confirmed by other investigators.¹⁷⁶ It has been documented that ionic dysfunction occurs with TBI and that extracellular K^+ is transiently increased as a result of the depolarization synchronous with mechanical insult.^{75, 121} This loss of ionic homeostasis should be accompanied by a concomitant movement of sodium. Seminal studies by Betz¹⁹ and Gotoh et al.⁵¹ measured unidirectional movement of sodium into brain following an ischemic injury, and work by Aldrich et al.⁴ has demonstrated a clear relationship between tissue water content and sodium accumulation in spinal cord injury. Traumatic brain injury is thought to trigger a cascade of events, including mechanical deformation, neurotransmitter release,⁷⁵ mitochondrial dysfunction,^{10, 28, 132, 192} and membrane depolarization,⁷⁵ that can lead to alterations in normal ionic gradients.¹²¹ Excitatory amino acids released via mechanical deformation and membrane depolarization can activate ligand-gated ion channels, which allow ions to move down their electrochemical gradients. In addition, membrane depolarization resulting from ionic flux and trauma may trigger voltage-sensitive ion channels, providing further routes for ionic movement.⁷⁵ These ionic disturbances are identified by an increase in extracellular K^+ with a concomitant decrease in extracellular Na^+ , Ca^{2+} ,

and Cl^- . Restoration of ionic homeostasis can either occur via energy-dependent co- and countertransport processes such as the Na^+ - K^+ adenosine triphosphatase, the Na^+ / K^+ /2 Cl^- cotransporter, the Na^+ - H^+ transporter, and the Na^+ - Ca^{2+} exchanger or via simple washout into the vascular or CSF compartment.^{9,19,116} It is reasonable to suspect that the net balance of ionic movement that accompanies brain injury results in the movement of cations out of the extracellular space into cells. The movement of Na^+ and Ca^{2+} is passively followed by Cl^- to maintain electroneutrality and is followed isosmotically by water. If sustained, these ionic disturbances result in cellular swelling and cytotoxic edema, which has been shown to be the primary contributor to raised ICP.

Effect of Hypothermia on Cellular Edema

Mild hypothermia on the order of 32°C has been shown to be neuroprotective. The question has been posed if part of this neuroprotection was due to the amelioration of cellular edema.¹¹⁵ It was observed that hypothermia itself was causing significant swelling of glial cells in a dose-dependent manner. In that study the authors reported that inhibition of the Na^+ / H^+ -antiporter with 50 μM 5N-ethyl-n-isopropyl-amiloride significantly reduced the hypothermia-induced cell swelling, indicating activation of the Na^+ / H^+ -antiporter. However, mild or moderate hypothermia failed to prevent cell swelling from other toxins (lactic acid, arachidonic acid, or glutamate), mediating the development of cytotoxic brain edema. As a result, it was considered that cerebral protection by hypothermia in vivo is most likely not attributable to an inhibition of cytotoxic brain edema.

Effect of Steroids on Brain Edema

Despite frequently encouraging experimental results concerning the effectiveness of steroids, particularly in the late 1960s, clinical trials of glucocorticoids in ischemic stroke, intracerebral hemorrhage, aneurysmal subarachnoid hemorrhage, and TBI have not shown a definite therapeutic effect.⁴⁹ The evidence supporting glucocorticoid therapy for spinal cord injury is controversial; however, methylprednisolone continues to be widely used in this setting.^{25–27,46,89,109,153,159,160,162,171,180} In contrast, in clinical trials for head injury and stroke, corticosteroids have not been shown to be effective in treating cellular edema.¹³⁹

Aquaporins and Their Pivotal Role in Edema

The recent discovery of AQP¹⁷⁸ was acclaimed enthusiastically, given that they may provide a mechanism for massive water movement across the cell membrane. Water permeability was considered to be a special case, because several criteria have been developed to distinguish between transport through pores or diffusion through the lipid bilayer. The identification of the AQP family, a water-conducting protein-based channel consisting of 11 subtypes ubiquitously distributed in tissues and organisms, was a landmark discovery. Despite a common molecular structure, mammalian AQP^s have been subdivided

into three functional groups according to permeability characteristics.¹⁸³ The AQP^s, including AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, are permeable to water. The aquaglyceroporins, including AQP3, AQP7, and AQP8, are permeable to water, glycerol, and urea. The neutral solute channels, including AQP9, are permeable to water, glycerol, urea, purines, pyrimidines, and monocarboxylates. The AQP10, like AQP9, is permeable to water and neutral solutes but is not permeable to urea and glycerol.⁵⁸ The AQP^s are ubiquitously distributed in mammalian tissue. To date, the following six AQP subtypes have been described in rodent brain: AQP1, AQP3, AQP4, AQP5, AQP8, and AQP9.^{12,42,120,181,193} Of the six AQP subtypes described in rodent brain, much of the data come from AQP4, one of the first subtypes described in the central nervous system. Aquaporin-4 is expressed in the astroglial endfeet membranes adjacent to blood vessels.¹¹⁹ It was observed around all vessels of any size in white and gray matter and in all brain structures currently being studied: forebrain, diencephalons, midbrain, and brainstem.^{12,181} Nicchia et al.¹¹⁸ reported that AQP4 was responsible for the fast water transport of cultured astroglial cells and might be a primary factor in ischemia-induced cerebral edema. Moreover, it was observed that mice lacking AQP4 were partially protected from brain edema in water intoxication and ischemic models of brain injury.¹⁸³ In a seminal article, Manley et al.¹⁰³ further showed in AQP4-deficient mice a 35% decrease of cerebral edema following middle cerebral artery occlusion, as measured by the percentage of hemispheric enlargement. Alterations in the expression of AQP4 in cultured rat astrocytes during hypoxia and reoxygenation were also noted.¹⁹³

Investigators have also reported that an increase of water content in the brain after intraperitoneal injection of distilled water and 8-deamino-arginine vasopressin was greatly delayed in dystrophin-null transgenic mice.¹⁷⁸ It was also noted in this work that the dystrophin-associated proteins are essential for proper localization of AQP4 protein in brain. These results indicated that AQP4 may play a key role in modulating brain water transport and raised the possibility that AQP4 inhibition could provide a new therapeutic option for reducing brain edema in a wide variety of cerebral disorders. Nevertheless, electron crystallographic analysis of the 3D structure of AQP1 revealed an hourglass-shaped channel with 8-Å apertures at both ends and a central constriction (3 Å in diameter).¹¹⁶ With this configuration, only water molecules in a chain, not solutes, pass successively through the narrow channel. Aquaporins are thus a simple water channel whose upregulation increases the water filtration coefficient of the membrane and allows the passage of water in either direction along the osmotic gradient secondarily to the regulatory or recovery processes. The specific anatomical and cellular localization of the AQP4 water channel, localized on the astrocytic endfoot, has been implicated in playing a major role in water balance.¹⁸¹ The finding by Manley et al.¹⁰³ that AQP4 deletion in knockout mice reduces brain edema after acute water intoxication and ischemic stroke implicates new avenues for treatment, particularly if pharmacological modulation of AQP4 is possible. It has been demonstrated in the laboratory that AQP4 can be modulated pharmacologically,^{8,86,87} but more work is needed before translating these results to the patient.

Regulation of AQP4 Following Injury

There is some evidence, however inconsistent, regarding regulation of AQP4 after brain injury. In different models inducing neuronal degeneration, AQP4 mRNA was upregulated following BBB disruption.¹⁸⁵ In a combined head injury model, AQP4 immunostaining was negative and the AQP4 mRNA downregulated in areas with impaired BBB.⁷⁸ Following cortical impact injury, hemispheric ipsilateral AQP4 was progressively downregulated within the first 48 hours.⁷⁷ Similar results were found following ischemia and hypoxia,¹⁹³ all known to produce a predominantly cytotoxic edema.

Clearance of Vasogenic Edema

The processes involved in the resolution of vasogenic edema are better understood than those of cellular edema. Fluid moves through the interstitium via both bulk flow and diffusion processes.^{122,124} In vasogenic edema clearance, three possible mechanisms have been considered to be responsible for clearance of extracellular water: 1) migration of extracellular water to the CSF by bulk flow in the presence of pressure gradients;^{85,143,144} 2) glial uptake of the protein components of edema fluid;^{45,188} and 3) reverse vesicular transport from the blood via transendothelial passage.¹⁸⁶ Authors of studies have shown that the primary route for clearance of a proteinaceous fluid is the CSF pathway.^{52,124} These findings support earlier results by Reulen and colleagues,¹⁴⁴ who demonstrated movement of edema fluid toward the ventricle. In other studies^{123,124} it was noted that during the infusion of fluid into the parenchyma when the edema is pressure driven, the fluid traveled to the cortex by three paths: the extracellular space of the neuropil, the expanded pericapillary space around microvessels, and the expanded perivascular space. The possibility that materials are eliminated by drainage along perivascular channels into the CSF in the subarachnoid space has been reported.³³ Findings of our studies would also suggest that the perivascular spaces of venules and veins are the primary pathway for the efflux of solutes from the brain parenchyma to the CSF space.¹²²⁻¹²⁴ A striking observation in these infusion studies was that neither astrocytes nor neurons were observed to take part in the clearance process, which is in contrast to reports that cellular uptake of protein was the major mechanism for clearance of vasogenic edema.⁸⁵

The Role of AQPs in Edema Clearance

Papadopoulos et al.¹²⁸ demonstrated in mice killed immediately after 60 minutes of continuous intracerebral infusion that AQP4-null mice developed higher ICP and brain water content compared with wild-type controls. Aquaporin-null mice have reduced brain swelling and improved neurological outcome in models of cellular edema including water intoxication, focal cerebral ischemia, and bacterial meningitis.^{102,183} However, if studied only during the infusion process, the processes of resolution may be misleading as clearance of extracellular edema takes considerable time.^{122,124} Interestingly, AQP9 was upregulated in astrocytes surrounding ischemic lesions, suggesting that AQP9 may play a role in the regulation of

postischemic edema.¹¹ The role of the AQPs in the clearance process of edema remains to be clarified. In a model of intraparenchymal injection of lipopolysaccharide, it was observed that the first signs of barrier disruption coincided with a strong induction of AQP4 mRNA in perivascular glial cells. Restoration of the barrier was associated with high induction of AQP4 mRNA in parenchymal reactive astrocytes and perivascular glial processes, suggesting that high levels of AQP4 mRNA may be beneficial under these circumstances.¹⁷⁰

Imaging Techniques Used in Identifying the Type of Edema

It is possible with the aid of MR imaging techniques to measure the diffusion of water in brain tissue. This is usually expressed as the ADC. A reduction in ADC is interpreted as a decrease in diffusion, whereas an increase in ADC is associated with an increase in diffusion. In cellular edema, the water is more closely bound and thus it would be expected to result in a decreased ADC. To test this, cytotoxic edema secondary to acute hyponatremia was induced with intraperitoneal injections of 2.5% dextrose in water and a subcutaneous injection of arginine vasopressin.¹⁵⁶ It was observed that the ADC was significantly reduced, and plots of ADC compared with total brain water showed a statistically significant inverse linear relationship between ADC and increasing brain water, indicating that ADC may be a sensitive indicator of cytotoxic brain edema and may enable quantitative evaluation of edema using diffusion-weighted imaging. In a photochemical model of cerebral infarction, ADC was measured and was found to be elevated in nonischemic tissue but was diminished in areas with histological evidence of ischemic damage or necrosis.¹⁵⁶ Similarly, reduced ADCs were found in the rodent middle cerebral artery model of ischemia, and ADCs were positive when fluid was infused into the parenchyma simulating an extracellular edema.⁶⁶ In other experimental studies, the temporal change of water following closed head injury was followed acutely and over 14 days using MR imaging ADC methods.¹⁷ In these studies, ADC was positive, signifying a vasogenic edema during the first 60 minutes postinjury. However, after this rise, the ADC steadily decreased and was minimal by 7 days postinjury. This study provided supportive evidence that cellular edema played a major role in traumatic brain swelling.¹⁶ Other studies in which the authors used diffusion tensor in models producing vasogenic and cytotoxic edema were correlated with histological findings, and diffusion tensor was found to be altered based on the edema subtype.⁹³⁻⁹⁵

Summary and Recommendations

Considerable effort has been expended in understanding the pathophysiology of brain swelling, and it is now clearer that increased brain tissue water and not vascular engorgement plays the most important role in the swelling process leading to raised ICP, reduced CBF, and potential herniation. We now appreciate that the abatement of the edematous process will depend on the type of edema that is contributing to tissue swelling. Extracellular or vaso-

genic edema production is driven by barrier dynamics following injury. Treatments such as hypothermia, which will suppress prolonged secondary opening of the barrier, may prove to be effective therapies. The depth of hypothermia, its duration, and ideal rates of rewarming have yet to be established.^{1,3,32,37,43,65,69–71,82,83,101,104,110,134–137,157,158,163,}

^{166,168,169,172,173,184,189,196,198} Decompressive craniectomy, which allows the brain to expand as it continues to swell, may also be effective in trauma and continues to be under careful study in the clinical setting.^{23,34,149} Perhaps the most exciting new findings that speak to both the control of production and resolution of edema in both trauma and ischemia are the recent studies by Manley and colleagues¹⁰³ and others who have focused on AQP science.^{5–8,12,39,86,87,102,117,118,127–129,177,183,193} These water channels offer hope for modulating and abating the devastating effects of fulminating brain edema.

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