



The pathophysiology of brain edema and elevated intracranial pressure

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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 well documented that in head injury, swelling leads to an elevation in intracranial pressure (ICP), which is a frequent cause of death, and to very poor prognosis in survivors. This swelling process has been classified into four distinct degrees of severity based on studies of the Traumatic Coma Data Bank. Of great importance is the fact that the degree of swelling assessed on the first CT scan, obtained soon after injury, is highly correlated with outcome ($P < .0002$).

■ BRAIN SWELLING—EDEMA OR VASCULAR ENGORGEMENT?

Our experimental and clinical studies provide strong evidence that *edema* is primarily responsible for the swelling process. For the past several decades, it has been generally accepted that the swelling process accompanying traumatic brain injury is mainly due to vascular engorgement, with blood volume providing the increase in brain bulk and subsequent rise in ICP. Edema was thought to play a minor role. However, our recent findings indicate that edema, not vascular engorgement, is responsible for brain swelling and that blood volume is actually reduced following traumatic brain injury. Thus, it is important to shift our attention to brain edema and to understand the pathophysiologic mechanisms responsible for water movement into brain.

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■ TRAUMATIC BRAIN EDEMA—VASOGENIC OR CELLULAR?

By definition, edema is an abnormal accumulation of fluid within the brain parenchyma; it is subdivided into vasogenic and cytotoxic types. Vasogenic edema is defined as fluid originating from blood vessels and accumulating around cells. Cytotoxic edema is defined as fluid accumulating within cells as a result of cell injury. The most common cytotoxic edema occurs in cerebral ischemia. Neurotoxic edema is a subtype of cytotoxic edema caused by high levels of excitatory amino acids. Heretofore, the edema specific to traumatic brain injury has generally been considered to be of “vasogenic” origin, secondary to traumatic opening of the blood-brain barrier. However, all three forms of edema can coexist, and their relative contributions to brain swelling and elevated ICP have not been identified. This is a critical problem, as effective treatment will clearly depend on the type of swelling.

Our own studies in this area are in sharp contrast to the general belief that traumatic brain injury results in a predominantly extracellular edema secondary to blood-brain barrier opening. Although a vasogenic component may be present, we strongly suspect that the type of swelling in traumatic brain injury with or without associated mass lesion is predominantly a cellular edema. A lack of barrier opening in the presence of continued swelling has been noted in our clinical studies of head-injured patients in whom magnetic resonance “water maps” were obtained with gadolinium challenge. Experimentally, we have strong evidence that the type of swelling in diffuse injury is predominantly cellular.

■ IONIC DYSFUNCTION IN BRAIN INJURY

It is well documented that ionic dysfunction occurs with traumatic brain injury and that extracellular K^+ is transiently increased as a result of the depolariza-

tion synchronous with mechanical insult. This loss of ionic homeostasis should be accompanied by a concomitant movement of sodium. The seminal studies by Betz et al and Gotoh et al measured unidirectional movement of sodium into brain following an ischemic injury, and work by other investigators has demonstrated a clear relationship between tissue water content and sodium accumulation. As we have demonstrated a predominantly cellular swelling, the extension of our work to the study of ionic movement is fundamental to a deeper understanding of the formation of traumatic brain edema.

Traumatic brain injury triggers a cascade of events, including mechanical deformation, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization, that leads to alterations in normal ionic gradients. Excitatory amino acids released via mechanical deformation and membrane depolarization activate ligand-gated ion channels, which allow ions to move down their electrochemical gradients. In addition, membrane depolarization resulting from ionic flux and trauma triggers voltage-sensitive ion channels, providing further routes for ionic movement. These ionic disturbances are identified by an increase in extracellular potassium ($[K^+]_{\text{ecc}}$) with a concomitant decrease in extracellular sodium ($[Na^+]_{\text{ecc}}$), calcium, and chloride.

Restoration of ionic homeostasis is accomplished via cotransport and countertransport processes such as the Na^+K^+ ATPase, $Na^+/K^+/2Cl^-$ cotransporter, Na^+-H^+ transporter, and Na^+-Ca^{2+} exchanger. However, if the injury is severe, or if secondary insults occur, disruption of ionic homeostasis persists as the cotransport and countertransport processes are impaired and become incapable of returning ion concentrations to their normal levels. Moreover, in the absence of adequate levels of ATP resulting from either an ischemic reduction in cerebral blood flow or insufficient production of ATP due to mitochondrial dysfunction, energy-dependent ion pumps and cotransport and countertransport processes are inefficient in counteracting the normal dissipative flux of ions down their electrochemical gradients.

We hypothesize 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 sodium and calcium is passively followed by chloride to maintain electroneutrality, and is followed isosmotically by water. If sustained, ionic disturbances result in cel-

lular swelling and cytotoxic edema, which we have shown to be the primary contributor to raised ICP. In traumatic brain injury, the initiating factors, which result in the movement of ions, may differ from those primarily responsible in ischemia. For example, ATP reduction may not be due to decreased cerebral blood flow since blood flow in traumatic brain injury persists and delivery of substrate is maintained.

■ LABORATORY MODELS OF TRAUMATIC BRAIN INJURY WITH BRAIN SWELLING

The study of traumatically induced swelling in the laboratory has been difficult, in part because of a lack of models that produce marked, rapid swelling and, most important, a steady rise in ICP. Fluid percussion, or direct dural impact, results in a sudden rise in blood pressure that is sufficient to breach the blood-brain barrier and is not suitable for the study of edema produced by closed head injury. Moreover, ICP increases only transiently and declines over time. Similarly, the classic model of subdural hematoma, which has been used by many investigators, also produces only a transient rise in ICP followed by a gradual recovery toward baseline.

For diffuse injury, we solved this problem with our development of a rat impact-acceleration model that develops marked swelling, a profound diffuse axonal injury, and a steadily rising ICP when secondary insults are superimposed upon the mechanical trauma. For mass lesions, we found that superimposing a controlled subdural hemorrhage following impact-acceleration injury resulted in similar effects. This combination, which mimics the clinical scenario better than a subdural hemorrhage alone, results in a remarkable, steady increase in ICP to greater than 50 mm Hg.

■ MAGNETIC RESONANCE TECHNOLOGY: DIFFUSION-WEIGHTED IMAGING TECHNIQUES AND PROTON SPECTROSCOPY

It is not possible to differentiate between vasogenic (extracellular) and cytotoxic (cellular) edema by conventional tissue water measurement. In vivo diffusion-weighted imaging is a magnetic resonance technique that, by employing strong magnetic field gradients, is sensitive to the random molecular translation of water protons. Maps of the apparent diffusion coefficient (ADC) can be derived from a series of diffusion-weighted images obtained with

different magnetic fields. Recent findings in experimental ischemia models suggest that ADC values can provide earlier and more specific information about tissue damage and characteristics of edema. Several studies have adopted this concept in distinguishing the type of edema in ischemia and traumatic brain injury. The application of such new imaging techniques can quantify the temporal changes and document the type of edema that is occurring during both the acute and the late stages of edema development.

■ N-ACETYLASPARTATE ASSESSED BY PROTON SPECTROSCOPY AND MITOCHONDRIAL DYSFUNCTION

We hypothesize that mitochondrial dysfunction prevents the restoration of ionic and cell volume homeostasis. Hovda's group has clearly implicated ionic shifts as the major mechanisms for cellular and organelle swelling. Moreover, Muizelaar has recently demonstrated in rat brain suspensions that mitochondrial function was profoundly reduced after traumatic brain injury and that this was largely calcium-dependent. Povlishock has posited that the shear and tensile forces of injury induce mechanical poration of cell membranes that can cause an "excitatory amino acid storm" that leads to intracellular calcium influx with subsequent mitochondrial loading. It is envisioned that in a permissive environ-

ment, such calcium loading leads to mitochondrial permeability transition, which is linked to overt mitochondrial failure. The accuracy of this assumption is supported by several studies. More importantly, studies by Povlishock et al have shown that cyclosporin A, which blocks mitochondrial permeability transition, translates into significant neuroprotection.

N-acetylaspartate (NAA) was discovered in 1956 by Tallan, More, and Stain and is represented by the largest peak in a proton spectrum (^1H MRS). It is synthesized in mitochondria from L-aspartate and acetyl-CoA in a reaction catalyzed by an N-acetyltransferase. NAA has been found histochemically to be a constituent of neurons and axons, with lesser amounts in glial cells. Large numbers of studies show NAA absent or reduced in brain tumor (glioma), ischemia, degenerative disease, and inborn errors of metabolism, and it is accepted fact that NAA levels correspond to tissue damage. Studies of NAA in severe brain injury are relatively few, and the temporal course of NAA changes in trauma in association with ADC values has not been studied. Because NAA is synthesized by the mitochondria, it is reasonable to posit that reduced tissue NAA will be associated with regions of low ADC, low ATP, ionic dysfunction, and brain edema. This report describes the most recent information available on NAA reduction in human head injury.