Cerebral Edema in Traumatic Brain Injury

Pathophysiology and Prospective Therapeutic Targets

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KEYWORDS

• Cerebral edema • Traumatic brain injury • Pathophysiology • Therapeutic targets • Blood-brain barrier

KEY POINTS

- The development of cerebral edema following TBI is an important factor which contributes to evolution of brain injury following initial trauma.
- Post-traumatic cerebral edema arises from disruption of the blood-brain barrier or dysfunction of cellular ionic pumps and may be classified as vasogenic or cytotoxic edema, respectively.
- Vasogenic and cytotoxic edema arise from unique molecular pathways which which may be targeted therapeutically in pre-clinical models.
- Future studies are needed to determine which therapies targeting cerebral edema may have clinical efficacy in human TBI.

INTRODUCTION

Traumatic brain injury (TBI) is a complex and heterogeneous disorder with a tremendous public health burden. It is grossly defined as an alteration in brain function or other evidence of brain pathology caused by an external force which may occur in a multitude of settings – including the highway, at home, at work, during sports activities, and on the battlefield.[1,2] Despite extensive measures taken to prevent these injuries, TBI continues to have an unacceptably high morbidity and mortality. As of 2010, the Centers for Disease Control and Prevention estimated that 2.5 million emergency department visits, hospitalizations, or deaths were associated with TBI, either alone or in combination with other injuries. TBI was a diagnosis in more than 280,000 admissions. A total of 1.7 million people each year sustain a TBI in the United States. Of those, 275,000 are hospitalized and 52,000 die. It is thought that TBI is a contributing factor in nearly a third of all injury-related deaths in the United States.[3] Furthermore, many of those individuals who survive their initial injury will have clinically evident disability later in life; it has been estimated that up to 5.3 million people are currently living with TBI-related disability in the United States alone.[4]

The deleterious effects of a TBI are not confined to the initial traumatic event. Initial brain trauma initiates a complex cascade of pathophysiologic pathways that lead to evolution

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of brain injury.[5] These effects have led to the adoption of the crude temporal categories of injury known as primary and secondary injury. Primary injuries are brain injuries that occur at the time of the initial trauma, including cerebral contusions, diffuse axonal injury, penetrating or tissue crushing wounds, extra-axial hematomas, and damage to the cerebral vasculature.[5,6] Short of preventive measures to mitigate and/or avoid initial injury, in the absence of regenerative therapy very few, if any, therapeutic options are available to reverse injury. Secondary injuries are those that occur in the hours to days following the initial insult and are composed of a diverse array of pathophysiologic phenomena, including hypoperfusion, mitochondrial dysfunction, oxidative injury, as well as disruptions to the blood-brain barrier (BBB).[5–8]

One process central to the pathogenesis of secondary injury is the development of cerebral edema.[9] In accordance with the Monro-Kellie Doctrine,[10] an increase in brain volume as a result of cerebral edema rapidly leads to an increase in intracranial pressure (ICP). As brain volume begins to increase, cerebrospinal fluid (CSF) is displaced into the spinal thecal sac and blood is compressed from the distensible cerebral veins with little increase in ICP. Once these compensatory mechanisms are exceeded, ICP increases exponentially—a common deleterious cascade observed in severe TBI—and has been shown to correlate with increased mortality and poor functional outcomes.[11] Increases in ICP, in turn, lead to the compression of brain vasculature and decrease the cerebral perfusion pressure, defined as mean arterial blood pressure subtracted by ICP. Mechanical compression of the vasculature and/or reductions in cerebral perfusion pressure may give rise to either focal or global ischemia, which may lead to further edema and ultimately irreversible brain injury.[12]

Evolving brain edema also leads to the genesis of pressure gradients across different intracranial compartments and mechanical displacement of brain structures across compartments, a phenomenon known as *herniation*. This herniation leads to further neurologic injury through axonal stretch, vascular disruption or compression, and/or a combination thereof and often represents a penultimate event to significant neurologic injury, coma, or death. Despite its importance in neurologic decline, treatment of traumatic intracranial hypertension predominately consists of hyperosmolar therapy, for example, hypertonic saline and mannitol, which lead to the efflux of water from the brain into the systemic circulation and/or surgical decompression. Efforts to expand the treatment armamentarium for intracranial hypertension, including hypothermia and barbiturate induced coma, have largely been unsuccessful. In the present article, the authors focus on the cellular and molecular mechanisms underlying cerebral edema following TBI derived from review of both clinical and preclinical animal models. Special attention is devoted to the cellular and molecular mechanisms underlying its pathogenesis as well as future therapeutic targets.

PATHOGENESIS OF CEREBRAL EDEMA

Cerebral edema is broadly categorized as being either vasogenic or cytotoxic.[13,14] Vasogenic edema results from disruption to the BBB formed by cerebrovascular endothelial cells (ECs) and leads to an influx of protein-rich fluid from circulating blood into the brain interstitial fluid.[15] Cytotoxic edema, on the other hand, is a product of failure of homeostatic ion channels and pumps resulting in failure of ionic gradients and an intracellular osmotic shift resulting in cellular swelling, a process more prominent in astrocytes and glial cells.[16,17]

TBI is a complex and multifaceted injury that leads to dysfunction and/or disruption of multiple cell types.[5] Although TBI-associated brain edema was initially thought to arise predominantly from vasogenic mechanisms, more recent clinical and preclinical studies have demonstrated that cytotoxic edema plays a significant role.[18–20] For example, MRI studies of patients with closed-head injury revealed a mixed picture of both cytotoxic and vasogenic edema by imaging criteria.[21] However, in the absence of vasogenic edema, a process that depends exclusively on cytotoxic edema would be self-limiting.[22] Similarly, it is likely that the contributions of vasogenic and cytotoxic processes make differential relative contributions through different phases of evolution of edema following brain trauma. In TBI, brain edema is thought to follow a bimodal time course, with one study showing that half of patients had their highest mean ICP recorded during the first 3 days after injury, whereas 25% of patients showed their highest mean ICP after postinjury day 5.[23] In the ensuing subsections, the authors describe in detail the molecular and cellular mechanisms underlying the pathogenesis of posttraumatic vasogenic and cytotoxic edema.

The Blood-Brain Barrier and Neurovascular Unit

The BBB is formed by a continuous lining of brain ECs with specialized properties.[24,25] Tight junctional complexes composed of transmembrane occludin and claudin proteins are linked