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EDEMA AND BRAIN TRAUMA

A. W. UNTERBERG,[a]* J. STOVER,[b] B. KRESS[c] AND K. L. KIENING[a]

[a]*Department of Neurosurgery, Ruprecht-Karls University of Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany*

[b]*Department of Surgery, Division of Surgical Intensive Care Medicine, University Hospital Zurich, Zurich, Switzerland*

[c]*Division of Neuroradiology, Ruprecht-Karls University of Heidelberg, Heidelberg, Germany*

Abstract—Brain edema leading to an expansion of brain volume has a crucial impact on morbidity and mortality following traumatic brain injury (TBI) as it increases intracranial pressure, impairs cerebral perfusion and oxygenation, and contributes to additional ischemic injuries.

Classically, two major types of traumatic brain edema exist: "vasogenic" due to blood–brain barrier (BBB) disruption resulting in extracellular water accumulation and "cytotoxic/cellular" due to sustained intracellular water collection. A third type, "osmotic" brain edema is caused by osmotic imbalances between blood and tissue. Rarely after TBI do we encounter a "hydrocephalic edema/interstitial" brain edema related to an obstruction of cerebrospinal fluid outflow.

Following TBI, various mediators are released which enhance vasogenic and/or cytotoxic brain edema. These include glutamate, lactate, H^+, K^+, Ca^{2+}, nitric oxide, arachidonic acid and its metabolites, free oxygen radicals, histamine, and kinins. Thus, avoiding cerebral anaerobic metabolism and acidosis is beneficial to control lactate and H^+, but no compound inhibiting mediators/mediator channels showed beneficial results in conducted clinical trials, despite successful experimental studies. Hence, antiedematous therapy in TBI patients is still symptomatic and rather non-specific (e.g. mannitol infusion, controlled hyperventilation). For many years, vasogenic brain edema was accepted as the prevalent edema type following TBI. The development of mechanical TBI models ("weight drop," "fluid percussion injury," and "controlled cortical impact injury") and the use of magnetic resonance imaging, however, revealed that "cytotoxic" edema is of decisive pathophysiological importance following TBI as it develops early and persists while BBB integrity is gradually restored. These findings suggest that cytotoxic and vasogenic brain edema are two entities which can be targeted simultaneously or according to their temporal prevalence.

Key words: blood brain barrier, brain edema, traumatic brain injury, cerebral perfusion pressure, intracranial pressure, aquaporin.

*Corresponding author. Tel: +49-6221-566300; fax: +49-6221-565534.
E-mail address: andreas.unterberg@med.uni-heidelberg.de (A. W. Unterberg).

Abbreviations: ADC, apparent diffusion coefficient; AQP4, Aquaporin4; BBB, blood–brain barrier; CBF, cerebral blood flow; CCII, controlled cortical impact injury; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial blood pressure; TBI, traumatic brain injury.

One characteristic feature of patients with severe traumatic brain injury (TBI) is "brain edema" as diagnosed by routine CT scans. Despite its complexity, Pappius (1974) defined brain edema as an increase in net brain water content which leads to an increase in tissue volume. Intense research conducted in the past decades resulted in a refined characterization of this rather simple definition. In this context, brain edema is influenced by a concert of complex molecular and cellular, structural and functional changes in blood–brain barrier (BBB) function, microcirculation, cell volume regulation and autodestructive mediators. These alterations may develop independently and converge in common pathological pathways.

Due to the limited intracranial space any additional increase in intracranial volume as related to progressive brain edema formation aggravates the already impaired compliance and contributes to additional ischemic injuries due to reduced perfusion and oxygenation. This, in turn, critically influences and determines the patients' fate.

The aims of this paper are to characterize the different types of brain edema developing after TBI, to summarize most recently discovered pathophysiological mechanisms, and to suggest possible therapeutic targets.

Classification of brain edema

At the turn of the last century, Reichardt (1905) introduced the term "brain edema" to distinguish from "brain swelling" thought to arise from vascular engorgement. In the 1960s the neuropathologist Klatzo (1967) using a "cold injury" model described two major types of brain edema, the cytotoxic or vasogenic edema related to intracellular or extracellular water accumulation due to cellular injury or BBB breakdown, respectively. In 1975 Fishman (1975) added these the "interstitial edema" observed in patients with hydrocephalus, a condition primarily not of decisive importance during the acute phase following TBI. A fourth type of brain edema is the "osmotic" edema caused by imbalances of osmotic active substances (e.g. sodium), promoting water influx into cells. The details and characteristics of vasogenic, cytotoxic and osmotic brain edema following TBI will be presented (Table 1).

Vasogenic brain edema

The functional integrity of the BBB is of fundamental importance for the maintenance of normal brain volume and cerebral homeostasis. Its structural and functional impairment, in turn, drives vasogenic brain edema. BBB damage can be caused by mechanical injury, autodestructive mediators, or both.

Reese and Karnovsky (1967) using electron microscopy and horseradish peroxidase identified the cerebral

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Table 1. Characteristics of different traumatic brain edema (BE) types

	Vasogenic BE	Cytotoxic BE	Osmotic BE
Development	Increased permeability of capillary endothelial cells caused by tissue necrosis (BBB disruption)	1. Increased cell membrane Na^+/K^+ permeability	Osmotic gradient (plasma → tissue)
		2. Na^+/K^+-ATPase failure	
		3. Uptake of osmotically active solutes	
Permeability	Increased	Unchanged	Unchanged
Edema fluid	Rich in protein	No proteins	No proteins
		Rich in electrolytes	Rich in electrolytes (tissue hyper-osmolality)
			Low in electrolytes (serum hyposmolality)
Morphology	No cell swelling	Cell swelling	Cell swelling
	Increased interstitial space	Decreased interstitial space	

endothelial cell lining as the anatomic correlate of the BBB which is functionally influenced by the adjoining astrocytes. The cerebral endothelial cells differ in many ways from endothelial cells in other organs as they are sealed together by tight junctions, thus preventing uncontrolled passage of proteins. The scarce intracellular vesicles suggest little transcellular vesicular transport (Mollgard and Saunders, 1986). Vasogenic brain edema is characterized by a protein-rich exudate derived from plasma resulting from an increased permeability of the capillary endothelial cells to albumin and other plasma proteins (Betz et al., 1989).

Cytotoxic brain edema

Cytotoxic brain edema is characterized by sustained intracellular water accumulation involving both astrocytes and neurons. In contrast to vasogenic brain edema, this type of edema occurs independently of the BBB integrity.

Three mechanisms—either singly or in combination—account for neuronal and glial cell swelling:

1. increased Na^+ and K^+ permeability of the cell membrane
2. energy depletion followed by a failure of the active ion-pumps as e.g. Na^+/K^+-ATPase
3. sustained uptake of osmotically active solutes

A simplistic model to describe this type of cell swelling is "pump-leak-equilibrium disturbance." Under physiological conditions, the influx of osmotic active solutes (especially Na^+) is balanced by their active, energy-dependent elimination via the Na^+/K^+-ATPase. This inhibits an intracellular accumulation of osmotically active solutes and prevents a consecutive influx of water and otherwise ensuing cell swelling. Under pathological conditions, as encountered following sustained neuronal activation and cell lysis following TBI, increased uptake of Na^+ causes a shift in the "pump-leak-equilibrium," which cannot be compensated by the active Na^+/K^+-ATPase. Concomitant or progressive energy depletion during ensuing cerebral ischemia related to structural as well as functional mitochondrial impairment propagates Na^+/K^+-ATPase failure and aggravates cytotoxic brain edema.

Sustained disturbance in electrogenic and electrochemical stability early after TBI is predominantly influenced by the excitatory neurotransmitter amino acid glutamate (Schneider et al., 1992; Staub et al., 1993). Activation of post- and presynaptic ionotropic and metabotropic glutamate receptors as well as glial and neuronal glutamate transporters is associated with a dramatic influx of water binding Na^+, H^+, Ca^{2+}, Cl^- and H^+ ions which contribute to ensuing neuronal and glial cytotoxic edema formation. In this context, the stereotypic stoichiometry of 3 Na^+, 1 H^+, 1 Cl^- cotransport and antiport of one K^+ ion per glutamate molecule reflects continuous shift of water from the extracellular to the intracallular space during normal and uncontrolled neuronal activity (Amara and Fontana, 2002). Neuronal and glial efforts to maintain or re-establish an electrolyte equilibrium may lead to energy depletion and failure of cell volume control which is further compromised by Ca^{2+}-mediated activation of intracellular second messenger cascades resulting in increased oxygen free radicals and arachidonic acid metabolites (Gegelashvili and Schousboe, 1997). Glutamate uptake is regulated by changes in transporter expression and activity which are modulated kinetically by phosphorylation, membrane trafficking, oxidative processes, membrane potential and ion gradients (Amara and Fontana, 2002; Gegelashvili and Schousboe, 1997).

While neuronal glutamate uptake may indirectly control neuronal activation by reducing the amount of synaptically released glutamate it is predominantly the responsibility of astrocytes to clear the extracellular space to prevent uncontrolled neuronal firing caused by glutamate overload within the synaptic cleft. As neurons are outnumbered by astrocytes (20:1 in humans, 10:1 in rats) and can swell five times their normal size it is obvious that glial swelling is the main mediator of brain edema (Kimelberg, 1995). Furthermore, the specific anatomic distribution and characteristic functions of glial cells accentuate the detrimental influence of structural and functional glial impairment. In this context, decreases in glial glutamate transporters (van Landeghem et al., 2001) are accepted to contribute to the persistent

significant increase in extracellular glutamate levels early after TBI.

Osmotic/interstitial brain edema

Osmotic brain edema is neither vasogenic nor cytotoxic by nature. The speed at which osmotic imbalances develop is of decisive importance since concentration or dilution of osmolarity within the brain can only be compensated if osmolar gradients develop slowly. Of utmost clinical relevance in the clinical setting is the "syndrome of inappropriate secretion of anti-diuretic hormone" generating an osmotic imbalance (serum hyposmolarity) and causing osmotic brain edema. On the other hand, osmotic brain edema may also arise if cerebral tissue is in a hyperosmolar state as observed after cerebral ischemia. Under such conditions, reperfusion with isotonic fluids may cause an additional water flux into the reperfused tissue. This pathophysiological pathway was observed following TBI as necrotic brain tissue sampled from the central area of contusion during surgery exhibited a very high osmolality, thus inducing osmotically driven fluid accumulation (Katayama and Kawamata, 2003).

Ischemia and brain edema

Following TBI we frequently observe ischemic injuries. Ischemic as well as traumatic brain edema involves both cytotoxic and vasogenic brain edema. As long as cerebral blood flow (CBF) does not drop below a critical threshold, cerebral water and electrolytes remain normal even if electrophysiological disturbances are already present ("non-critical ischemia"; Hossmann and Schuier, 1980). Below this threshold, water and electrolyte homeostasis is disturbed ("critical ischemia"). Brain edema may develop when CBF decreases below a threshold of about 10 ml/100 g/min. At this "low flow status," ion exchange pumps break down. Thereafter and in the case of irreversible tissue damage, BBB breakdown occurs allowing extravasation of serum proteins and vasogenic brain edema development. Thus, ischemic brain edema is initially cytotoxic (cellular) and later vasogenic in nature.

If ischemia is absolute and CBF approaches zero, e.g. during a cardiac arrest, intracellular water accumulation develops within a few minutes. It was found that after 1 h of total ischemia in cats the extracellular space is significantly reduced while total water content and intracranial pressure remained unchanged (Schuier and Hossmann, 1980). This indicates a shift of water from the extracellular into the intracellular space. The interval by which vasogenic edema supervenes is not clearly defined. During the initial 3–6 h of ischemia the BBB remains impermeable to the passage of conventional barrier tracers such as Evans Blue.

However, it has to be mentioned that after onset of ischemia—despite cell swelling—no *net increase* of water is present as long as CBF is not reestablished. Only after reperfusion there is a rapid increase in extracellular fluid and a corresponding rise in intracranial pressure (ICP) as well as brain water content.

In *complete ischemia followed by reperfusion,* cellular/cytotoxic brain edema dominates and BBB remains intact as demonstrated by the absence of Evans Blue extravasation. Several hours after ischemia, the BBB becomes permeable to serum proteins and blood serum extravasates into the brain leading to vasogenic brain edema formation. Two factors mainly contribute to the timing of these phases, the severity and duration of CBF reduction and the timing of CBF restoration ("reperfusion injury"; Avery et al., 1984).

In contrast to complete ischemia–reperfusion injury such a biphasic brain edema formation is absent in *incomplete ischemia*. Within the first 4–12 h after incomplete ischemia, cytotoxic brain edema develops. Without reperfusion there is no rapid brain edema progression despite a delayed BBB breakdown (Betz et al., 1989).

Traumatic brain edema

TBI comprises a variety of cerebral lesions, including hematoma, subarachnoid hemorrhage, contusions and diffuse axonal injury. Development of traumatic brain edema depends on the type of primary lesions and associated conditions, like arterial hypotension, hypoxia or even ischemia.

The traditional view of the past decades was that brain edema following trauma is predominantly vasogenic due to BBB opening, particularly in and around contusions. For many years research of traumatic brain edema focused on cryogenic injury models with a necrotic focus surrounded by leaky vessels. This view was supported by the CT appearance of contusions presenting as hyperdense hemorrhagic lesions in the early period after trauma followed by the development of a hypodense halo around the hemorrhagic focus (Fig. 1). This assumption had also been criticized since administration of contrast enhancing compounds in MRI/CT studies did reveal only minimal or moderate BBB leakage (Bullock et al., 1990).

Traumatic brain edema can be further characterized by its extent and distribution ranging from perifocal (regional) to diffuse (generalized) which may also present as a continuum.

Focal/perifocal traumatic brain edema

A traumatic cerebral contusion is characterized by a hemorrhagic core with necrotic tissue that is poorly or no longer perfused. Perfusion within the surrounding perifocal tissue is also significantly diminished. During the initial 2–3 days following TBI brain edema progresses from the core and incorporates primarily uninjured tissue adjacent to the lesion (Fig. 1; Bullock et al., 1990; Bareyre et al., 1997; Stroop et al., 1998; Unterberg et al., 1997).

As mentioned before this type of lesion and brain edema has previously been modeled by inducing a focal cryogenic lesion to the cortex. While the induced brain edema is vasogenic in nature it only conditionally mimics the clinical situation. A continuous growing body of evidence gained by numerous experimental studies involving the "controlled cortical impact injury" (CCII) model (Dixon et al., 1991) has revealed that focal as well as perifocal traumatic brain edema is predominantly cytotoxic. In this model an accelerated bolt hits the cortex producing a focal

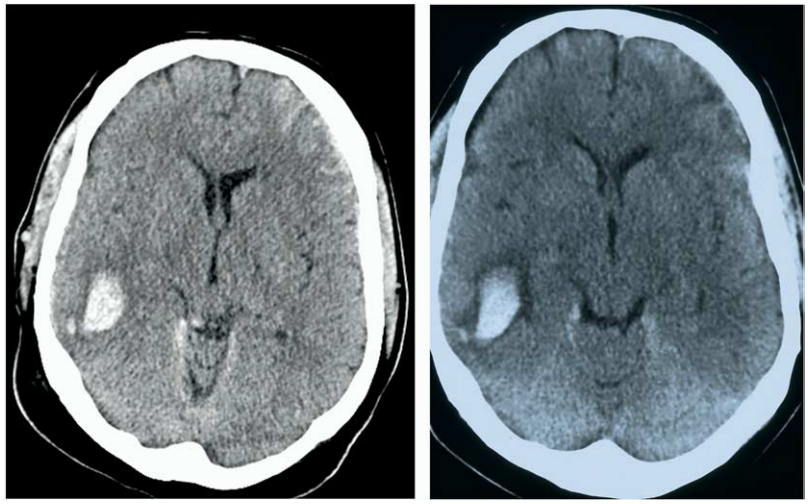

Fig. 1. CT scans of a hemorrhagic contusion of a severely head-injured adult. At 6 h after TBI (left) the lesion is hyperdense only demarcating the hemorrhagic core. By 36 h, the lesion is surrounded by a perifocal halo (area of low density), consisting of both vasogenic and predominantly cytotoxic brain edema.

necrosis which is surrounded by a progressively growing edematous zone. MR studies including diffusion weighted imaging and mapping of the apparent diffusion coefficient (ADC) clearly demonstrated decreased ADC values indicative of cellular/cytotoxic brain edema (Fig. 2; Stroop et al., 1998; Unterberg et al., 1997). Additional studies indicated only transient and moderate BBB opening in the perifocal zone (Stroop et al., 1998).

Using an impact acceleration model ("weight drop trauma"; Foda and Marmarou, 1994; Marmarou et al., 1994) a significant increase in ADC and brain water content was observed during the first 60 min postinjury. This was associated with an increase in extracellular fluid volume and vasogenic brain edema resulting from BBB opening. The transient ADC increase was followed by a continuing decrease in ADC starting 45 min after trauma, reaching a minimum value by 7 days after injury. In this subacute stage water content continued to increase indicating the predominance of cytotoxic brain edema (Barzo et al., 1997; Marmarou, 2003).

Clinical data also strongly support the concept of a cellular brain edema. MRI studies in patients with TBI within the first 24 h after injury revealed no evidence of BBB leakage; moreover, in focal injuries, ADC was increased only within the core of the contusion, but was reduced distal to the lesioned side indicating cellular brain edema (Kawamata et al., 2000; Maeda et al., 2003). At this point it is important to mention that ADC represents the algebraic sum of vasogenic (increased ADC values) and cellular (decreased ADC values) brain edema. Interestingly, decreased ADC values were measured within the perifocal tissue surrounding human contusions with CBF values clearly above ischemic thresholds (Marmarou, 2003). Although it is extremely difficult at the moment to draw a clear conclusions regarding the nature and time course of various brain edema components in the experimental and clinical settings, it has become evident that cytotoxic brain edema is of significant importance.

Diffuse traumatic brain edema

As stated earlier, ischemia may play a role in TBI and can appear at all stages of the disease, both globally and regionally. The resulting initial brain edema is mostly intra-

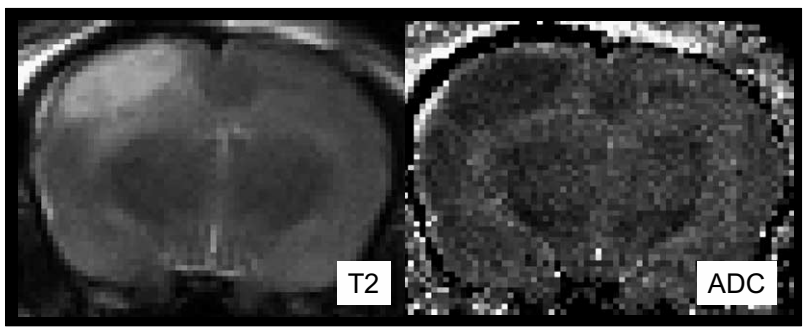

Fig. 2. MRI studies characterizing brain edema following focal experimental contusion in rats. T2-weighted sequence and ADC mapping (ADC calculated from diffusion weighted images) indicate intracellular water accumulation (decreased ADC values) within the cortical contusion (hyperintense area).

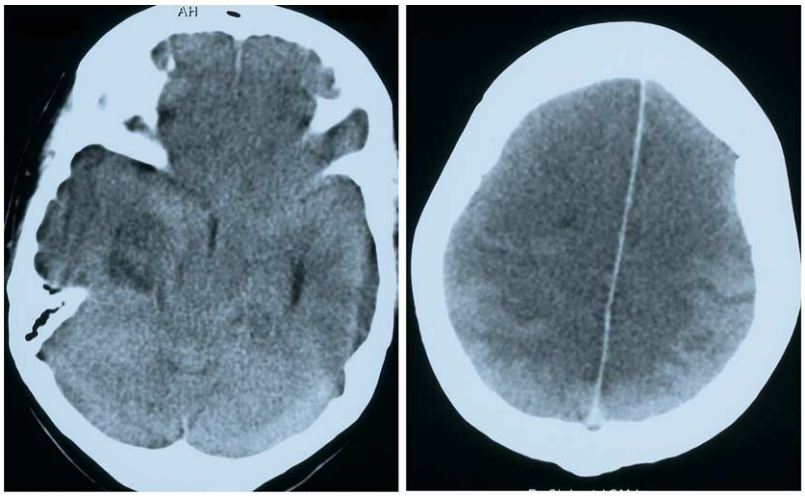

Fig. 3. CT scan of a severely head-injured patient with diffuse brain swelling obtained 70 h following TBI. The lateral ventricles are narrow, the basal cisterns are compressed (left), gyri and sulci are no longer discernible (right).

cellular, e.g. cytotoxic, and more "diffuse," i.e. not related to focal lesions. While autopsy studies indicated that a high percentage of patients revealed ischemic lesions (Graham et al., 1989) and ultra-early CBF studies following trauma indicated reduced CBF in many patients (Bouma et al., 1992), recent positron emission tomography studies gave no support for the assumption of a critically reduced CBF in a subacute stage after trauma (Diringer et al., 2000, 2002). Thus the impact of ischemia in TBI remains controversial.

In a series of diligently designed measurements in humans Marmarou et al. (Marmarou et al., 2000) proved that the major component contributing to traumatic brain swelling and increased ICP is not vascular engorgement, i.e. an increased cerebral blood volume, but rather a decreased CBF. Thus swelling as well as increased ICP is related to diffuse cytotoxic brain edema. A typical example of diffuse brain edema is given in Fig. 3.

Treatment of traumatic brain edema: Novel approaches

Today treatment of traumatic brain edema is still largely symptomatic. All treatment modalities presently used are directed at decreasing ICP. The most effective treatment strategy is to administer osmodiuretics (mannitol) which create an osmotic gradient dehydrating particularly vital, well-perfused cerebral structures.

Other modalities, like hyperventilation, hypothermia, and barbiturate coma are used to decrease cerebral blood volume by decreasing CBF due to vasoconstriction or decreased metabolism.

To date, we still lack a potent drug to attenuate traumatic brain edema formation and progression. This also holds true for steroids which were postulated to seal the endothelial lining, thus attenuating vasogenic brain edema formation. The prevalence of cytotoxic edema formation which was previously underestimated might explain the limited efficacy of steroids to treat traumatic brain edema.

Nevertheless, the sedulous search for anti-edematous compounds has unveiled novel pathological pathways and pharmacological targets.

In past decades numerous series of experiments could demonstrate that traumatically injured tissue releases substances that enhance both vasogenic and cytotoxic brain edema. Such mediators are among others, glutamate, H^+ ions, K^+ ions, Ca^{2+} ions, arachidonic acid and its metabolites, oxygen free radicals, histamine, and kinins (for review see Schilling and Wahl, 1999; Unterberg and Sarrafzadeh, 2000).

Therefore, it is not astonishing that potent inhibitors affect brain edema development, at least experimentally. Clinically, however, no beneficial effects could be seen following administration of amino steroids, superoxide dismutase, calcium antagonists, bradykinin receptor inhibitors, or various glutamate receptor antagonists (Bullock et al., 1999). In the past decade, the field of glutamate-mediated excitotoxicity was considered most promising since non-competitive (e.g. aptiganel, dextrorphan) and competitive inhibitors (e.g. selfotel, d-CPPene) as well as allosteric modulators of postsynaptic ionotropic glutamate receptor channel complexes (polyamine, glycine, zinc, magnesium) proved beneficial in animal stroke and TBI models. While many compounds passed tolerability studies the majority of the initially tested agents caused undesirable and adverse neuropsychological and cardiovascular side effects (e.g. prolonged QT time, hypotension). Despite consideration of other potential targets based on promising experimental studies (e.g. immunophilin and mitochondrial pore blockers, serotonin receptor agonists, caspase inhibitors, promotors of neurotrophic potential, regeneration and neurogenesis; Royo et al., 2003), ionotropic glutamate receptor antagonists are still considered potential targets in ongoing phase I and II/III clinical studies using CP101-606, dexanabinol, and S-1746 (Doppenberg et al., 2004).

More recent experimental efforts shall be touched on briefly.

The *vasogenic* component could be reduced effectively by a specific bradykinin receptor antagonist (Plesnila et al., 2001), a metalloproteinase inhibitor (Kawai et al., 2003), a vitamin E derivative (Ikeda et al., 2000b) and L-histidine (Ikeda et al., 2000a) which interferes with oxygen free radicals.

The list of substances that prevent, inhibit or treat the *cytotoxic* type of brain edema produced following CCII, impact acceleration, and fluid percussion is rather long and comprises numerous substances and mechanisms: cannabinoid receptor modulators (Panikashvili et al., 2001), bradykinin antagonists (Stover et al., 2000b), a K^+ channel opener (Cheney et al., 2001), citicoline (Baskaya et al., 2000), enoxaparin (Wahl et al., 2000) and cyclosporine (Fukui et al., 2003).

To date, the most promising potential is attributed to cannabinoid receptor agonists that are presently undergoing clinical trials (Knoller et al., 2002). In addition, the concept to inhibit inflammatory processes by administering tacrolimus has attracted considerable interest (Stover et al., 2001). Again, a summary of these experimental studies in various models is extremely difficult and the overall picture is far from clear.

Future directions and pharmacological directives might be unveiled by inhibiting presynaptic metabotropic glutamate receptors (Stover et al., 2000a) and modulating glial (GLT-1, GLAST-1) and neuronal (EAAT3, EAAT4) glutamate transporters and the recently discovered vesicular glutamate transporters (VGLUT1-3; Fremeau et al., 2004).

Cerebral perfusion pressure (CPP) and traumatic brain edema

Following severe TBI, patients are at risk of developing secondary cerebral ischemic damage mainly due to raised ICP or arterial hypotension resulting in insufficient CPP. This, in turn, compromises CBF as well as tissue oxygenation and gives rise to brain edema progression contributing to evolving structural and functional tissue damage. This, in turn, negatively affects the neurological outcome. Consequently, maintaining a sufficient CPP, e.g. by increasing mean arterial blood pressure (MAP) is a widely accepted therapeutic strategy after severe TBI (The Brain Trauma Foundation, 2000). Under conditions of preserved cerebral autoregulation increasing MAP may reduce elevated ICP due to arteriolar vasoconstriction (Rosner et al., 1995). On the other hand, increasing MAP and CPP to the upper limit of the autoregulatory capacity known for its intra- and interindividual variability over time may promote brain edema formation and thus, increase ICP (Marshall et al., 1969; Schutta et al., 1968).

In addition to these effects on MAP and ICP, administration of vasopressors may directly interfere with brain edema development.

Following CCII, dopamine significantly increased brain edema despite sufficient CPP restoration, in both the ipsi- and contralateral hippocampus and temporal cortex. This occurred in the absence of ADC changes, pointing to a "vasogenic-like" brain edema component with extracellular water accumulation (Beaumont et al., 2000). Possible causes for this dopamine-induced aggravation of brain edema are increased neuronal excitation/excitotoxicity, thrombin-induced platelet accumulation, neurochemical alterations in the hypothalamo-hypophyseal pathway, transmembrane ion exchange and/or local alterations of vascular tone.

Opposed to the latter mentioned findings, Kroppenstedt et al. (2002) observed no edema progression after CCII neither with dopamine nor with norepinephrine administration. On the other hand, increased electroencephalographic activity as well as increased pericontusional glutamate and interleukin-6 (Stover et al., 2003) concentrations might foster mechanisms of secondary injury and additional brain edema formation.

Overall, a clear view concerning the impact of vasopressor therapy on traumatic brain edema is still pending.

Current concepts of traumatic cytotoxic brain edema development

As mentioned above, cytotoxic brain edema is the predominant cause of brain swelling after TBI (Kimelberg, 1995; Stroop et al., 1998; Marmarou et al., 2000; Barzo et al., 1996). It has been suggested that propagation of traumatic cytotoxic BE is not only caused by ischemia since brain edema develops despite sufficient CBF (Marmarou et al., 2000), but may arise due to direct mechanical injury inducing mitochondrial impairment, irrespective of cerebral perfusion. In this context, *N*-acetyl-aspartate, a neuron-specific metabolite synthesized by mitochondria and ATP were simultaneously reduced in animals subjected to a severe impact acceleration model (Signoretti et al., 2001). Mitochondrial dysfunction induces energetic impairment and excessive Ca^{2+} overload. In conjunction with an increased opening of the mitochondrial permeability transition pore resulting in a loss of the transmembrane electrogenic gradient, oxidative phosphorylation is uncoupled and mitochondrial swelling becomes inevitable. The ensuing ATP deficit results in a failure of ion pumps and a breakdown of membrane stability which, in turn, leads to uncontrolled swelling of neurons and astrocytes.

The recently detected cerebral Aquaporin4 (AQP4), a bidirectional transmembrane water channel localized among others in astrocytic end feet may play a crucial role in aggravation/resolution of traumatic cytotoxic brain edema.

Physiologically, AQP4 works with inward rectifying K^+ channel Kir4.1, co-localizing with AQP4 in astrocytic end feet of rodent astrocytes, thus clearing both water via AQP4 and K^+ ("K^+ siphoning") via Kir4.1 in high neuronal activity from the extracellular compartment to neighboring astrocytes and furthermore to the astrocytic syncytium (Nagelhus et al, 1999).

In pathophysiological situations, this concept has been challenged by the fact that dissociation of AQP4 from Kir4.1 expression can occur (Saadoun et al., 2003). Moreover, apart from cooperation with Kir4.1, AQP4 moves water across cell membranes *bidirectionally* along osmotic gradients.

A most significant finding relating to edema development is that AQP4 localization in astrocytic end feet is dystrophin-regulated as dystrophin-null mice showed delayed brain edema development pointing to AQP4 protein mislocalization (reduction of AQP4 protein in astroglial end feet but unaltered total AQP4 protein; Vajda et al., 2002).

However, there is no doubt that decreased AQP4 counteracts progression of brain edema as AQP4 k.o. mice showed significantly reduced brain edema and decreased mortality after water intoxication as well as following middle cerebral artery ligation, while BBB remained intact (Manley et al., 2000). AQP4/AQP4mRNA upregulation occurred in wild type mice after water intoxication (Vajda et al., 2000) and in high grade astrocytomas/brain metastasis, where BBB opening and vasogenic brain edema is present (Saadoun et al., 2002). Further hints of involvement of astrocytic AQP4 in traumatic cytotoxic brain edema has been demonstrated by Marmarou (2003) and Amorini et al. (2003). First, they demonstrated that i.v. radio-active labeled Na^+ (Na^{22}) increased after TBI which was obviously cleared intracellulary as tissue microdialysis fluid did not show an increase in Na^+ (Marmarou, 2003; Doppenberg et al., 2004). Secondly, after application of protein kinase C activators causing AQP4 inactivation (Nakahama et al., 1999), both Na^{22} and water content were reduced providing support to the notion that AQP4 dependent pathways for Na^+ and water exist in astrocytes contributing to cytotoxic brain edema.

In experimental ischemic models AQP4/AQP4mRNA is reduced within the first 48 h after onset (Sato et al., 2000; Yamamoto et al., 2001) while marked upregulation occurs at later time points (Taniguchi et al., 2000). A similar pattern was found after CCII in rats. A stepwise reduction of AQP4 on the traumatized hemisphere over time was observed with a significant decrease at 48 h post trauma (Kiening et al., 2002). However, investigations on local AQP4 regulation after TBI did not add to a consistent picture. Ke et al. (2001) found AQP4mRNA downregulation in the contused cortex 24 h after trauma, while upregulation occurred in the more distant, ipsilateral basal ganglia and contralateral cortex. To the contrary, Sun et al. (2003) showed a significant decrease in AQP4mRNA pericontusionally with an upregulation adjacent and distant to the lesion following CCII.

While AQP4 is capable to drive brain edema we still lack a full understanding of the role of AQP4 under pathological conditions. Moreover, the functions of AQP1, 5, and 9 also located in astrocytes (Arima et al., 20203; Badaut et al., 2001, 2002, 2003; Yamamoto et al., 2002), are unknown, and the interaction of AQP's located in close neighborhood to astrocytes (e.g. ependyma, neurons, blood vessels) structures as well as the significance of tetrameric assembling of both AQP4 splice variants to "orthogonal array of particles" (Rash et al., 1998) and their further agglomeration require further research.

CONCLUSIONS

In principal, traumatic brain edema by itself is reversible. However, it remains a crucial factor to strongly influence the acute phase following severe TBI as it may increase ICP, decrease cerebral perfusion and brain oxygenation, and eventually lead to brain herniation and death. Consequently, treatment of traumatic brain edema remains a therapeutic challenge.

Ongoing identification of intra- and intercellular pathways will allow us to progress toward a more specific and maybe temporally adapted anti-edematous treatment of traumatic brain edema.

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