Aquaporins and Brain Edema

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Aquaporins are a family of transmembrane proteins that selectively allow the passage of water through the plasma membrane. Their importance is highlighted by their ubiquitous presence from bacteria to mammals. In humans, they are found throughout the body and recent work has highlighted their function within the brain. They are intimately involved in the production of cerebrospinal fluid and the control of water movement at the blood-brain barrier. Aquaporin levels are up-regulated in animal models of trauma, stroke and water intoxication as well as around human malignant brain tumors. They have thus been implicated in the formation of brain edema. Knock-out mice, without the aquaporin gene, appear to have reduced brain edema compared to their wild type brethren in models of brain edema. Currently, the clinical treatment of brain edema is limited. Increased knowledge of the aquaporins may open new targeted therapies for brain edema. © 2004 Elsevier Inc. All rights reserved.

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Aquaporin, brain edema, AQP1, AQP4

Increased tissue water content, or edema, can occur in any damaged tissue in the body. Cerebral edema occurs following a variety of insults: trauma, local and systemic infection or inflammation, infarction, and neoplasms. Although edema is tolerated in many tissues, its presence within the brain can result in increased intracranial pressure (ICP), which in turn, can significantly worsen neurologic outcomes. In adults, the intracranial volume is fixed owing to the rigidity of the skull. Normally, the intracranial space contains brain tissue, cerebrospinal fluid, arterial and venous blood. In addition, tumors, cerebral edema and traumatic hematomas increase the contents within the fixed intracranial cavity. The Monro-Kellie doctrine states that any increase in one component within the intracranial space does so at the expense of another. For example, a growing brain tumor displaces CSF caudally into the subarachnoid space surrounding the spinal cord. Blood is pushed into the extracranial vascular capacitance beds. However, once a certain size of the mass (tumor, edema, hematoma) is reached, the intracranial pressure (ICP) increases exponentially. Increased ICP places direct pressure on adjacent structures leading to decreased cerebral perfusion, resultant metabolic changes and infarction. This eventually leads to herniation of cerebral tissue and possible death. Therefore, increased ICP worsens neurologic outcomes. As cerebral edema complicates many of the aforementioned conditions, it can lead to drastic increases in ICP. Thus, cerebral edema can significantly worsen outcomes and lead to death following a variety of insults.

There are 2 broad classes of cerebral edema: cytotoxic and vasogenic [13]. Cytotoxic edema is an accumulation of intracellular fluid that occurs without disruption of the blood-brain barrier (BBB). Its location is primarily within gray matter where neurons and astrocytes are affected following trauma, ischemia, infarction or hypoxia. In contrast, when the BBB is disrupted, plasma leaks from capillaries into the interstitium and results in vasogenic edema. Vasogenic edema occurs with tumors and infarction, and is located primarily in white matter. Cytotoxic and vasogenic edema most likely represents a continuum as most pathologic processes may result in both types. For example, ischemia initially leads to cellular swelling (cytotoxic edema) with subsequent disruption of the BBB and resultant vasogenic edema [24].

Treatment of Cerebral Edema

Unfortunately, our ability to treat cerebral edema is modest. Osmotic agents such as Mannitol, decrease cerebral edema by creating an osmotic gradient favoring the movement of water from brain tissue to...
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Aquaporins General

Aquaporins (AQP) are a family of transmembrane proteins, which selectively allow the passage of water through the plasma membrane in fluid-transporting cell types throughout the body [16]. They are present from bacteria to mammals. They are small (MW ~30,000), and composed of 2 tandem repeats of 3 membrane-spanning alpha helices. The specificity for water appears to be determined by the size of the pore [7,11]. Although primarily permeable to water, some AQP’s may allow the passage of small solutes or ions.

There have been 11 aquaporins cloned to date [26]. Their distribution is widespread with AQP being located in: renal collecting ducts, secretory glands, skeletal muscle, stomach, liver, testes, and brain. Mutations in different AQP have been implicated in several human diseases. For example, AQP 2 is a vasopressin regulated water channel located within the collected ducts of human kidneys. Mutations in this gene result in hereditary nephrogenic diabetes insipidus [8]. In the eye, a type of cataract formation has been associated with a mutation in AQP0 [25].

**Aquaporins in the Brain**

Of the 6 aquaporins expressed in the brain, AQP1 and 4 are the most extensively studied and provide potential mechanisms for cerebral edema [3]. Normally, AQP1 expression is limited to the choroid plexus, the cerebrospinal fluid (CSF) producing cells within the ventricular system [17]. Thus it is thought to play a role in CSF secretion. Selectively blocking this channel in the choroid plexus may reduce CSF production and could potentially be used clinically to treat communicating hydrocephalus.

Although not normally found within brain parenchyma, AQP1 is extensively expressed within the cytoplasm of primary malignant brain tumors (astrocytomas). Furthermore, there appears to be greater AQP1 expression with increasing malignancy. Since increasingly malignant tumors have greater amount of cerebral edema on imaging studies, AQP1 expression may correlate with the extent of peritumoral edema. In contrast to astrocytomas, AQP1 is not found within metastatic carcinomas. However, AQP1 is present in the surrounding vascular endothelium and reactive astrocytes that accompany metastatic tumors [22]. As such, AQP1 expression may play a crucial role in the development of cerebral edema that complicates both primary and metastatic brain tumors. Blocking this channel could have beneficial effects on the vasogenic edema that accompanies brain tumors.

Unlike AQP1, AQP4 is normally present within the intravascular space. In addition, Mannitol can increase cerebral perfusion by improving red blood cell rheology via immediate plasma volume expansion [4] and can reduce ICP by reducing vascular volume following vasoconstriction [15]. However, Mannitol’s mechanism of action is a double-edged sword. With disruption of the BBB, as seen in vasogenic edema, Mannitol can pass into the brain parenchyma and exacerbate cerebral edema. This is of particular concern with repeated doses [12]. Thus, the usefulness of Mannitol is short lived and probably is best served as a treatment for acute increases in ICP.

Corticosteroids are thought to decrease vasogenic edema by decreasing capillary permeability. This is likely a direct mechanism on capillary endothelia through inhibition of phospholipase A-2 [19]. There is clearly a beneficial effect of corticosteroids on peritumoral edema [10,28]. Not only does the amount of edema decrease on imaging studies, but this translates into improved patient outcomes. Using steroids as the sole treatment in metastatic brain tumors doubles survival from 1 to 2 months [20]. Unfortunately, there has been no consistent benefit of steroids in head injury, thus limiting their use as a broad treatment for cerebral edema [2,6]. Corticosteroids also have systemic effects, which limit their usefulness. Although not born out by a recent meta-analysis, there are concerns that corticosteroids increase risk of infection and gastrointestinal bleeding [1].

In addition to the aforementioned medical treatments, cerebral edema can be treated surgically. Surgery to remove edematous brain tissue usually occurs in the setting of life threatening increases in intracranial pressure following craniocerebral trauma. Although surgery may be lifesaving, it is not targeted treatment and is usually used as a last resort. It is very difficult to know how much tissue should be resected; and regrettably, salvageable cortex is often removed. Thus surgery itself can result in significant morbidity despite its lifesaving value.

Ideally, treatment for cerebral edema would be targeted, have limited side effects, and be applicable to all types of edema. Such treatment does not currently exist. However, a newly discovered class of water channels, aquaporins, provide a new target for therapies directed at cerebral edema.
AQP4 is primarily expressed in glial cells at the blood-brain and the brain-CSF interfaces [9]. At the BBB, AQP4 is expressed within astrocytic foot processes adjacent to endothelial cells [17]. At the brain-CSF interface, AQP4 is found in the ependymal cells on the basal side of the plasma membrane. Given this preferential expression at fluid interfaces, it can be inferred that AQP4 plays an important role in water transport between fluid compartments within the brain. Astrocytes may utilize AQP4 to maintain extracellular homeostasis and protect neurons during osmotic challenges. Excess water would preferentially flow into astrocytes (not neurons) during hypertonic conditions. Swollen astrocytes could then return to normal during a regulatory volume decrease (a calcium dependent mechanism with extrusion of osmotically active solutes).

AQP4 has been demonstrated to play a role in the formation of brain edema in multiple pathologic states including tumors, trauma, water intoxication and infarction. As with AQP1, AQP4 upregulation occurs within malignant astrocytomas (primary brain tumors) and reactive astrocytes near metastatic carcinomas [22]. In addition, the expression of AQP4 correlates with the presence of contrast enhancement on computerized tomography (CT) scans, the latter being an indicator of BBB breakdown, and a conduit for cerebral edema. Thus, AQPs play a central role in the formation of vasogenic edema seen with malignant neoplasms. Therefore, selective blockage of AQP4 may help reduce the vasogenic edema in these clinical settings.

There is also excellent evidence that AQP4 plays a significant role in the formation of “cytotoxic” models of brain edema seen following trauma. Following traumatic cortical contusions in rats, the amount of AQP4 mRNA was significantly higher at the site of injury when compared to remote sites within the same brain [27]. Also, the degree of AQP4 expression correlates with the degree of brain edema as seen on magnetic resonance imaging (MRI). Interestingly, there was also a reduction of AQP4 expression in brain tissue adjacent to the site of injury [23]. The authors postulated that this represented a control mechanism to prevent rampant edema following brain injury. Such rampant edema, occasionally termed “malignant edema” occasionally follows trauma and can significantly worsen outcomes and even lead to death [5]. Thus, a lack of AQP4 down regulation in brain tissue adjacent to the trauma may be a mechanism for malignant edema.

Conclusions

Cerebral edema is a difficult problem complicating trauma, tumors, infections and infarctions of the brain. It can result in devastating morbidity and even mortality. Unfortunately, we are currently limited in our ability to treat edema, as many of our treatments are either ineffective or result in unacceptable side effects. Aquaporins appear to be intimately linked with the formation of brain edema and may therefore, provide a new potential target for treatment of this condition.

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Realists try to be as objective as possible. They try not to distort life by forcing it to agree with their own desires or with the formulas of art. However, in the process of selecting and presenting their material, they cannot help being influenced by what they feel and think. Even the most thoroughgoing Realism, therefore, is the result of observation and personal judgment.