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Drowning stars: reassessing the role of astrocytes in brain edema

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Edema formation frequently complicates brain infarction, tumors, and trauma. Despite the significant mortality of this condition, current treatment options are often ineffective or incompletely understood. Recent studies have revealed the existence of a brain-wide paravascular pathway for cerebrospinal (CSF) and interstitial fluid (ISF) exchange. The current review critically examines the contribution of this 'glymphatic' system to the main types of brain edema. We propose that in cytotoxic edema, energy depletion enhances glymphatic CSF influx, whilst suppressing ISF efflux. We also argue that paravascular inflammation or 'paravasculitis' plays a critical role in vasogenic edema. Finally, recent advances in diagnostic imaging of glymphatic function may hold the key to defining the edema profile of individual patients, and thus enable more targeted therapy.

Unclear waters in brain research?

Brain edema is a potentially fatal accumulation of fluid within the brain tissue, which can be caused by a range of medical conditions, including stroke, traumatic brain injury (TBI), brain tumors or metastases, meningitis, brain abscesses, water intoxication, altitude sickness, malignant hypertension, hypoglycemia, and metabolic encephalopathies [1]. In the current review, we will primarily discuss the acute causes of brain edema and refer to other texts for coverage on more chronic conditions such as peri-tumor edema [2,3].

Edema is a pathological phenomenon that may aggravate injury by either causing cellular dysfunction if fluid accumulates intracellularly, or by increasing the distance through which oxygen, nutrients and wastes have to diffuse when it is extracellular. Fluid build-up is more dangerous in the brain than in peripheral tissues for several macro- and microscopic reasons. Macroscopically, the brain is encased within a rigid skull causing any parenchymal swelling to increase intracranial pressure (ICP) and potentially compress other fluid compartments, such as the vasculature. This space limitation can set in motion a vicious cycle where elevated ICP compresses both capillary perfusion and venous drainage, which if unchecked, causes further edema, cerebral ischemia, brain herniation, and a lethal compression of brainstem cardiorespiratory centers. Brain edema can, therefore, be thought of as an intracranial compartment syndrome, and this global understanding forms the basis for core therapies such as trephination or surgical decompression, which have been practiced since ancient times [1].

Although several key molecular players that contribute to fluid accumulation have been identified in the last decade, our 'microscopic' understanding of brain edema is still incomplete. Key players likely include the water channel, aquaporin-4 (AQP4), the Na^+-K^+-Cl^- cotransporter 1 (NKCC1), sulfonylurea receptor 1 (SUR1)-regulated non-selective cation channels ($NC_{Ca\text{-}ATP}$), matrix-metalloproteinase 9 (MMP-9), thrombin, substance P, complement receptors, chemokine receptors (e.g., CCR2), and vascular endothelial growth factor (VEGF) (see Glossary) [2,4–6]. However, inhibiting or deleting some of these putative molecular targets can be both beneficial and detrimental, depending on when the treatment is initiated and the cause of the edema. We propose that these therapeutic heterogeneities can be at least partly explained by a previously unrecognized contribution from a brain-wide system for cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange, called the glymphatic pathway.

Composition of major water compartments in brain

To understand the molecular mechanisms that underlie brain edema, we first need to examine physiological water and ion homeostasis in the central nervous system (CNS) [3,7,8]. Water and solutes in the brain are distributed into four distinct fluid compartments separated by specialized cellular barriers: the intracellular fluid (ICF); ISF; CSF; and vascular compartments (Figure 1). CSF composition is primarily determined by the choroid plexus, and its production can be experimentally suppressed by inhibition of NKCC1 or carbonic anhydrase [9]. CSF contains a relatively high concentration of sodium to compensate for its low protein content [9]. ICF composition is energy-dependent and set up by the Na^+-K^+-ATPase and several co-transporters relying on the transmembrane Na^+ gradient that this pump generates, such as (Na^+)-K^+-Cl^-, glutamate, glucose, Na^+–H^+ and Na^+–Ca^{2+}-transporters [10]. The ICF composition in brain differs in several important respects between different cell types, broadly discussed here as neurons and glia (Table 1) [11,12]. Neurons, for

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Glossary

Aquaporin-4 (AQP4): plasma membrane water channel, belonging to the aquaporin family, and primarily expressed by astrocytes in brain on paravascular processes or end-feet.
Blood–brain barrier (BBB): a selective permeability barrier consisting of vascular endothelial cells and endothelial tight junctions that separates the central nervous system from the vascular compartment.
Convection: collective movement of water and solutes either as a result of diffusion and/or advection. The latter refers to bulk motion of the fluid driven by any combination of gradients (e.g., pressure, electrical, thermal, gravitational). In rare instances where the flow of a system = 0, then total convection ≈diffusion. However, in most biologically relevant situations where flow is high, convection ≈advection.
Cushing reflex: severely elevated intracranial pressure (ICP) can cause patients to develop bradycardia, irregular breathing, and increased blood-pressure.
Cytotoxic brain edema: swelling of brain cells due to a failure of cellular energy metabolism (i.e., intact blood–brain barrier). Examples include ischemic stroke and traumatic brain injury.
Diffusion: Redistribution of solutes from an area of high to an area of low concentration as a result of Brownian or random molecule movement. Diffusion flux increases as the concentration gradient becomes larger (Fick's first law) and decreases as a function of $\sqrt{}$molecular weight (Graham's law).
Diffusion versus advection: diffusion is a slow passive process that does not involve bulk movement of fluid, and is highly dependent on concentration gradient and weight of diffusing molecules. Advection relates to rapid directional movement of a fluid, which is largely independent of molecular weight and concentration gradients. Advection is thought to be the main mechanism governing interstitial fluid turnover in peripheral tissues, and likely also the brain [31,108].
Glymphatic system: paravacular fluid exchange pathway that enables brain interstitial and cerebrospinal fluid turnover and is facilitated by glial cells.
Hemorrhagic brain edema: brain swelling caused by a complete breakdown of the BBB with leakage of all vascular contents including red blood cells, usually in the context of a hemorrhagic stroke or traumatic brain injury.
Interstitial brain edema: an anatomical term used to describe brain swelling caused by fluid accumulation in the interstitial space, which can occur during both ionic and vasogenic edema.
Ionic brain edema: a functional term used to describe brain swelling caused by net influx of salts (primarily NaCl) and water from the vasculature and/or CSF. Examples include ischemic stroke and traumatic brain injury.
Na+-K+-Cl– cotransporter 1 (NKCC1): transmembrane cation-chloride transporter widely expressed in secretory organs, the choroid plexus, and at a lower level in both neurons and astrocytes.
Osmotic brain edema: a subtype of ionic edema where low blood osmolarity forces net water influx to the brain; for example, water intoxication, syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Penumbra: a region of perfused and potentially salvageable tissue surrounding the core of a brain infarct. The penumbra is often defined experimentally by staining for hypoxic tissue with 2,3,5-triphenyltetrazolium chloride (TTC) or clinically by examining the perfusion–diffusion mismatch (PDM) on MRI.
Starling's equation: Jv = Kf [(Pcapillary – Pinterstitium) – (πcapillary – πinterstitium)]; that is, net fluid movement (Jv) = filtration coefficient (Kf) × [(hydrostatic pressure gradient) – reflection coefficient (σ) × (oncotic pressure gradient)]. A recent reconsideration of this equation by Simard *et al.* has added separate filtration coefficients for hydrostatic and osmotic forces, to better reflect the unique properties of the BBB.
Sulfonylurea receptor 1 (SUR1)-regulated non-selective cation channels (NCCa-ATP): transmembrane cation channels that becomes activated following energy depletion and is linked to cytotoxic, ionic and vasogenic brain edema.
Vasogenic brain edema: a functional term used to describe brain swelling caused by increase BBB permeability, causing leakage of protein, water and salts. Examples include ischemic stroke, traumatic brain injury, brain tumor or metastasis, subarachnoid hemorrhage, and meningitis.
Virchow–Robin space (VRS): a term used for macroscopically visible extension of the subarachnoid space that ensheaths arteries as they penetrate the brain parenchyma. The VRS represents the proximal extension of the peri-arterial space implicated in the glymphatic system.

example, maintain a lower intracellular Cl^- concentration than glia through expression of KCC2, which is important for the hyperpolarizing effect of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) [13]. Glia have up to four-times greater water permeability due to enrichment with water channel aquaporin-4 (AQP4) [14]. ISF composition is dependent both on solutes exported from brain cells and exchange with CSF, and is very similar in composition to the latter. Conversely, the vascular

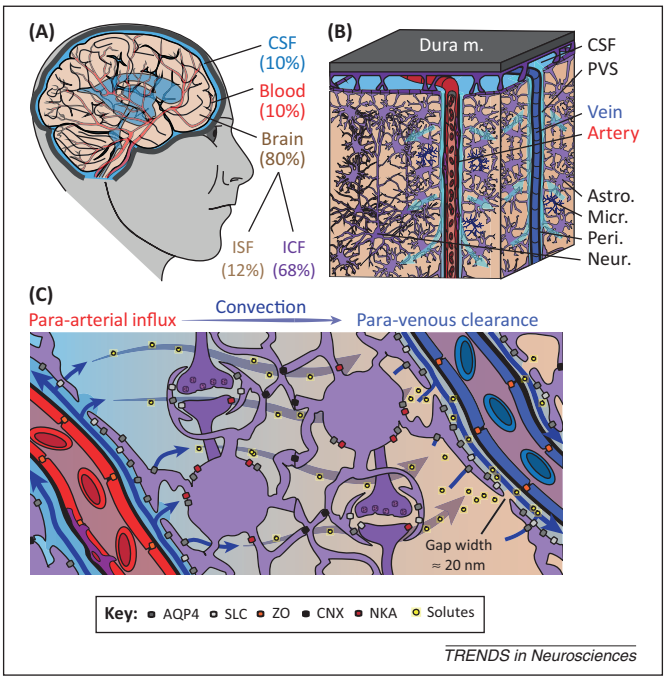

Figure 1. The glymphatic system regulates cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange in the brain. **(A)** Illustration of the main fluid compartments in the brain. **(B)** Diagram of fluid influx via penetrating arteries and efflux along a subset of large-caliber veins. **(C)** Diagram of proposed molecular mechanisms governing paravascular CSF–ISF exchange. Abbreviations: paravascular space, PVS; solute carrier, SLC; zonula occludens, ZO; connexin, CNX; and Na^+-K^+-ATPase, NKA; intracellular fluid, ICF; aquaporin-4, AQP4.

compartment is largely independent from all the other water compartments in the CNS due to the blood–brain barrier (BBB), which has a very low permeability to major osmolytes like Na^+, K^+ and Cl^-, and is impermeable to proteins [9,15].

Brain, CSF, and blood are separated by two concentric barriers

The different elements of the neurovascular unit are closely inter-dependent, and interrupting endothelial tight junctions, pericyte coverage, or astrocyte function alone can compromise the entire BBB [16–20]. The barrier function in most living vertebrates is thought to lie in the vascular endothelium, which expresses abundant tight junctions that prevent solute entry into brain [16,17,21]. Unlike in other organs, cerebral endothelial cells are entirely devoid of water channel aquaporin-1 (AQP1) and other aquaporins [3]. However, the cerebral endothelium has extensive transporter expression, along with a potential for selective vesicular transcytosis (pinocytosis) in pathological settings, which can flux large amounts of water along with ions, glucose and amino acids [9,22,23]. Most vertebrates also possess a second successive 'glial barrier' outside the blood vessel wall [24], which has arisen multiple times during evolution, yet its exact function has long been unclear [25]. In rodents, a recent electron micrographic 3D reconstruction found this second barrier consists primarily of astrocyte end-foot processes, covering 99.7% of the vasculature, with the remaining area being made up of small 20-nm inter-cellular clefts [26]. Pericytes and microglial processes are also scattered in between the vascular wall and astrocytic end-feet [26]. The dimensions of the intercellular clefts