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Muddying the water in brain edema?

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In their recent review in *TiNS*, Thrane *et al.* [1] discussed the role of a proposed ‘glymphatic’ system of convective solute flow in the pathology of acute brain edema. Controversies relating to the relative importance of convective versus diffusive transport in clearing toxic metabolic byproducts from brain parenchyma have been comprehensively reviewed elsewhere [2, 3] and it is not our intention to repeat the arguments made in these papers but, instead, to clarify aspects of the physiological function of the glial water channel aquaporin-4 (AQP4) and its contribution to brain edema that we believe have been muddled by the glymphatic hypothesis.

As originally stated [4], the glymphatic hypothesis pro-poses convective flow in brain parenchyma generated by hydrostatic pressure-driven *trans*-astrocytic water move-ment facilitated by AQP4 in perivascular endfeet. There are several problems with this hypothesis (Figure 1). First, the hydrostatic pressure is extremely small compared with the osmotic pressure generated by ion transport across cell membranes. Arterial wall pulsations that have been pro-posed to generate hydrostatic pressure in the paravascular space are on the order of 1 μ m [5]; modeling studies with larger wall displacements of 5 μ m suggest maximal hydrostatic pressure transients of approximately 1 kPa in the paravascular space [6], equivalent to the osmotic pressure generated by a 0.4-mOsm difference across the endfoot membrane. Osmotic gradients of 20 mOsm or more are routinely generated across the astrocyte plasma mem-brane in response to metabolic activity and K^+ redistribution, which provide the dominant driving force for water transport. A related issue is the ‘salt accumulation problem’ [3, 7], where pressure-driven water flow across a salt-impermeable membrane concentrates solutes on the high-pressure side and dilutes solutes on the low-pressure side, creating an opposing osmotic gradient that largely counter-acts the effectiveness of hydrostatic pressure in driving water transport within confined volumes. Furthermore, because AQP4 transports water only and is concentrated on the perivascular face of endfeet, where it facilitates uptake of water into the astrocyte and cellular swelling, it is hard to envision how convective flow across the endfoot itself could occur. Finally, the cell impermeant tracers used to track convective flow move through the small gaps between endfeet and not through the endfeet themselves. Any pulsation-driven flow into endfeet would reduce the driving force for convection through the gaps and, hence, tracer transport into the interstitial space. Therefore, pulsation-driven water flow through AQP4 in astrocyte endfeet is unlikely at physiologically relevant hydrostatic pressures and, if it did occur,

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would not be expected to generate convective flow in the interstitial space or increase tracer movement from paravascular cerebrospinal fluid (CSF) to interstitial fluid (ISF).

Application of the glymphatic hypothesis in the context of brain edema led Thrane *et al.* to propose that convective pumping of CSF into ischemic areas, rather than osmotic mechanisms, is responsible for acute edema following ischemia. As the authors indicate, studies to measure astrocyte volume changes using two-photon optical microscopy are limited by spatial resolution; however, electron microscopy consistently demonstrates endfoot swelling as an early consequence of ischemia [8, 9], supporting AQP4-mediated osmotic uptake of water into astrocytes during the early stages of edema. As the authors correctly point out, much remains to be understood about the functional significance of AQP4 enrichment in astrocyte endfeet, both in normal physiology and during edema. Experimental data suggesting that AQP4 facilitates fluid exchange between CSF and ISF are intriguing but difficult to interpret because of baseline differences in parenchymal extracellular volume fraction between wild type and AQP4-null mice [10, 11]. Quantitative studies have failed to find evidence for directional convective flow in cortical gray matter under normal conditions [12, 13], so perhaps the results of Iliff *et al.* [4] are a consequence of differences in extracellular space (ECS) structure between wild type and AQP4-null mice. Future studies of the role of AQP4 in diffusive and convective fluid transport in the brain will benefit from the application of quantitative imaging methods and biophysically realistic spatial modeling.

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Figure 1.

The glymphatic hypothesis versus conventional understanding of the role of aquaporin-4 (AQP4) in brain water movement. **(A)** The glymphatic hypothesis proposes a major role for hydrostatic pressure-driven water flow through astrocyte endfeet; conventionally, transmembrane flow in response to hydrostatic pressure is small compared with osmotic pressure gradients. **(B)** In the glymphatic model, water flows through endfeet through AQP4 to drive convection in the parenchyma; conventionally, water flow causes cell swelling (or shrinking) until osmotic equilibrium is reached. **(C)** In the glymphatic model, AQP4-

facilitated convective water flow drives directional movement of large solutes; conventionally, AQP4 regulates diffusion through effects on extracellular space (ECS) volume.

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