Commentary

A Disequilibrium Oncotic Model of Brain Fluid Flux

Jonathan Edwards[1,2]

1. University College London, United Kingdom; 2. University of London, United Kingdom

Application of the revised Starling model proposed by Levick and Michel (2010) suggests that cerebrospinal fluid (CSF) production is essential for maintenance of a low interstitial protein content in brain irrespective of any role in waste clearance. The anatomy of the brain, ventricles and choroid suggests that CSF enters brain by net bulk diffusion through both internal ependymal and external pial surfaces as part of a continual refreshment of low protein intertitium in the manner of a repeatedly squeezed sponge or mop, under forces such as arterial pulsation.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

Fluid flux within and around the brain is complicated and still lacks a simple intuitive explanation for many [1][2][3]. Recent work has focused on a perivascular 'glymphatic' system as a route for waste disposal [2], but uncertainties continue. The anatomical arrangement of choroid plexus and ventricles remains puzzling, especially if a historical account focused on convective CSF flux from choroid to arachnoid granulations is put into question [1][3].

In 2010, Levick and Michel [4] proposed a revision of the original Starling model of balanced vascular hydrostatic and oncotic pressures for fluid flux in other tissues. They argued that for an oncotic differential across blood vessel walls to be maintained in the presence of a small but necessary efflux of proteins, water efflux must occur so that tissue protein is constantly washed out. Starling forces might nearly balance but never exactly.

This disequilibrium model for oncotic control may also be useful in analysing brain fluid flux but may need some modification. In most tissues (not liver, kidney and brain) extracellular fluid pressure is slightly sub-atmospheric (~ -5mm Hg [5]), allowing concave body contours, with interstitium resembling a sponge milked of fluid by muscle activity and lymph hearts fed by 'wicking'. In contrast, brain

interstitium is at positive CSF pressure (5-15mm Hg [6]), close to that observed in venules elsewhere (10-20mmHg). With free drainage of venous sinuses by gravity, brain venules are likely to contain blood at a pressure little or no higher. Moreover, the oncotic differential in brain is perhaps the greatest of all tissues, with CSF protein levels being lower than most interstitium (0.5g/L versus 20g/L [5][7]).

Based on published figures, the net Starling force for brain venules (the level accredited with most water flux in other tissues) could be as much as ~20mmHg *inwards.* Brain vasculature might be expected, not to provide transudate to wash out tissue protein, but to reabsorb tissue water, leading to an interstitial protein level as high as, if not higher than, plasma. Even with a conservative estimate of net Starling forces nearer zero, there appears to be no means of achieving oncotic disequilibrium.

The very low protein level in CSF and the low permeability of brain blood vessels to protein (blood brain barrier) suggest that evolution has favoured mechanisms that support a particularly low brain extracellular fluid (ECF) protein content, presumably with one or more survival advantages. There are two obvious candidates. The intricate structure of brain tissue may benefit from excluding proteins like fibrinogen and immunoglobulin that in other tissues mediate events followed by structural remodelling or scarring. Low tissue protein content may also optimise ECF as an ionic sink background to neuronal membrane excitation.

If this is the case, there is an obvious role for CSF produced by choroid, with very low protein content, to wash out tissue protein and maintain disequilibrium. Choroid micro-vessel and epithelial architecture is adapted to high water efflux, involving active transportation [1]. In contrast, brain vessels may be adapted to minimise unhelpful water reabsorption.

Note, however, that the proposed requirement is for keeping ECF protein levels low, not removing ‘waste’. The protein may be functional and recyclable. Degraded protein may be handled, as in other tissues, by pinocytosis via scavenger receptors. Small metabolite waste needs to be rapidly cleared via venules, especially in a tissue with high metabolic activity.

In this approach the anatomy of choroid plexus, ventricles, subarachnoid space, inter-gyral fissures and perivascular canals all make sense. The ventricles are not channels for convective flow but baths with a large surface area deep inside brain through which low protein fluid, fresh from choroid, can pass, through permeable ependyma [1], into brain by directional bulk diffusion under an oncotic gradient (as opposed to random diffusion). Any local rise in brain ECF protein level from oncotic effects of plasma or protein efflux can be countered by this water influx. Since diffusion can occur throughout the

interstitium, low oncotic pressure can be restored rapidly across brain despite limited migration of individual water molecules.

Having the choroid in the lateral ventricles, connected to outer subarachnoid by a narrow opening, ensures that all internal spaces are subject to a slight hydrostatic opening force. If choroid was outside the brain these spaces would be subject to closing forces. The downside is a risk of hydrocephalus if there is blockage.

Similar uptake of low protein fluid would be optimised on the outer brain surface by free convective CSF distribution into subarachnoid space and inter-gyral fissures, with another extensive surface area for diffusional access to brain. Moreover, turgor produced by fixed hydrophilic elements in brain interstitium could assist in opening perivascular channels (as the turgor of florets in a growing cauliflower opens up crevices between) so that low protein fluid has another, even more intimate, access route to interstitium.

The analysis so far provides a rationale for choroid-derived CSF influx. However, the Levick/Michel model requires that protein is washed *away,* which will not occur via brain microvessels against a protein gradient. Over time, protein must be removed either by another route of fluid efflux, or possibly pinocytosis by meningeal cells. Recent studies suggest that CSF access to draining lymphatics may provide the main route out [2].

A question raised by glymphatic investigators [2] is why there should be directional flow in perivascular space favouring ingress of fluid on the arterial side and egress on the venular side and whether this requires valves in these channels, so far undiscovered. On the model proposed here, such valves are not necessary. In a sense, the brain interstitium itself, acting as a sponge rhythmically squeezed by vascular pulsations and maybe electrical activity, coupled on the venous side to an exit route (dural lymphatics), would be its own valve system. Flow direction might vary over short time frames but, longer-term, net influx on the arterial side and net efflux on the venous side (where lymphatics are accessible) would be expected.

The exact form of the CSF exit route to lymphatics appears uncertain. It cannot be a convective route of any calibre, since this would lead to collapse of CSF pressure. However, if dura can take up CSF into peri-lymphatic tissue matrix, the slightly mysterious process of lymphatic ‘wicking’ and lymph heart pumping could operate as for other tissues.

A general framing for this analysis might be in terms of division of labour for two major microvascular roles: exchange of small nutrient/metabolite molecules, and water flux/control of protein differentials. In

brain, roles are sharply divided between parenchyma and choroid. In other tissues, division of labour is less clear (there may still be vessel heterogeneity) or may reflect other specialised water flux roles, as in kidney or salivary gland.

In summary, a disequilibrium oncotic model for brain fluid dynamics may provide a satisfying account of the observed anatomy and flux findings. This includes a role for a glymphatic efflux system but in terms of oncotic control rather than waste disposal.

References

1. ^a, ^b, ^c, ^dMacAulay N (2021). "Molecular Mechanisms of Brain Water Transport." Nat Rev Neurosci. **22**(6):326–344. doi:10.1038/s41583-021-00454-8.
2. ^a, ^b, ^c, ^dRasmussen MK, Mestre H, Nedergaard M (2022). "Fluid Transport in the Brain." Physiol Rev. **102**(2):1025–1151. doi:10.1152/physrev.00031.2020.
3. ^a, ^bHjørnevik T, Eide PK (2026). "Water Exchange Across the Blood–CSF Barrier: A Systematic Review." J Cereb Blood Flow Metab. doi:10.1177/0271678x251413926.
4. ^Levick JR, Michel CC (2010). "Microvascular Fluid Exchange and the Revised Starling Principle." Cardiovasc Res. **87**(2):198–210.
5. ^a, ^bStewart RH (2020). "A Modern View of the Interstitial Space in Health and Disease." Front Vet Sci. **7**:609583. doi:10.3389/fvets.2020.609583.
6. ^Lyons MK, Meyer FB (1990). "Cerebrospinal Fluid Physiology and the Management of Increased Intracranial Pressure." Mayo Clin Proc. **65**(5):684–707.
7. ^Tan S, Goh R, Burton E, Bacchi S, Slee M (2023). "Cerebrospinal Fluid Protein: What Is a Normal Reference Range?" Intern Med J. **53**(11):2147. doi:10.1111/imj.16268.s.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.