Spring Cleaning:

Waste Clearance in the Human Visual Pathway

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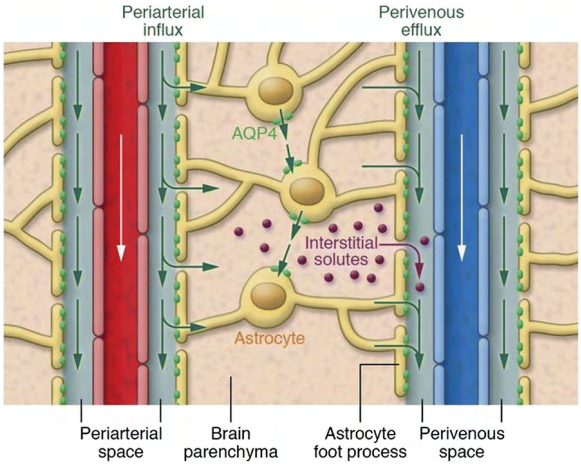
On October 5, 2022, Henrik Holvin Jacobsen defended his thesis "Extravascular Molecular Transport in the Human Visual Pathway" at the University of Oslo. The PhD project was conducted at the Dept. of Ophthalmology, Dept. of Neuroradiology, and Dept. of Neurosurgery at Oslo University Hospital. The main supervisor was Tiril Sandell, MD, PhD, with co-supervisors Morten C. Moe, MD, PhD; Geir Ringstad, MD, PhD; Per Kristian Eide, MD, PhD; and Øystein K. Jørstad, MD, PhD.

As the brain lacks a classic lymphatic system, the removal of waste products remained an enigma until the discovery of the glia-lymphatic (glymphatic) system in the rodent brain. In the glymphatic system, cerebrospinal fluid (CSF) and solutes are transported along paravascular spaces and exchanged with the extracellular compartment in the brain (**Figure 1**), facilitating the elimination of neurotoxic substances, such as amyloid β and tau protein. Accumulation of neurotoxic substances is central in the pathomechanism behind several degenerative diseases of the brain. Further, neurotoxins have been suggested in the pathomechanism of glaucoma and may harm the visual pathway, and an ocular glymphatic system has been recently discovered in which substances are cleared from the retina and into paravascular spaces in the optic nerve.



Key points:

- Novel in vivo findings suggest a glymphatic system in the human visual pathway.
- Reduced glymphatic transport in iNPH may imply impaired clearance of waste products from the visual pathway.
- The OCT parameters pBA and ONHH could potentially non-invasively predict elevated pulsatile ICP.

Figure 1. Schematic illustration of the glymphatic system. Fluid and solutes are transported along paravascular spaces on the arterial side and enter the interstitial space. The flux "flushes" through the interstitial space and drains into paravascular spaces on the venous side. The interchange occurs through specialized water channels (aquaporin-4) and gaps between the astrocytic end-feet. The green dots indicate the aquaporin-4 channels, and the arrows indicate the direction of flow. Reprinted from Ray, L., J.J. Iliff, and J.J. Heys, Analysis of convective and diffusive transport in the brain interstitium. Fluids and Barriers of the CNS, 2019. 16(1): p. 6 (permission obtained from the authors and through the Creative Commons Attribution License 4.0).

We explored the ocular glymphatic system in vivo in subjects with idiopathic normal pressure hydrocephalus (iNPH) and a reference group. iNPH is a neurodegenerative disease and a dementia subtype that shares clinical and histopathological features with other cerebral neurodegenerative diseases, such as Alzheimer's. iNPH has also been associated with glaucoma. Contrast was injected intrathecally and served as a marker for glymphatic transport. Following the injection, consecutive MRI scans were obtained to visualize the transport of gadobutrol in CSF and the visual pathway.

We demonstrated a direct communication between the CSF and the extravascular space in the visual pathway, suggesting the presence of a glymphatic system in the visual pathway. Further, we demonstrated that this transport was delayed in subjects with iNPH. These are the first in vivo observations suggesting glymphatic transport in the human visual pathway and that this is impaired in subjects with iNPH. Impaired transport may imply decreased clearance of potentially neurotoxic compounds from the visual pathway.

In the second part of this thesis, we studied the role of optical coherence tomography (OCT) as a tool for non-invasive estimation of intracranial pressure (ICP). Although small, there is a risk of serious complications associated with invasive ICP monitoring. We demonstrated that two OCT parameters—peripapillary Bruch's membrane angle (pBA) and optic nerve head height (ONHH)—were able to differentiate between elevated and non-elevated levels of pulsatile ICP. The pBA reflects the relationship between intraocular pressure and ICP, known as the trans-laminar pressure difference. The ONHH may serve as a surrogate for the optic nerve head volume. Pulsatile ICP reflects the intracranial pressure waves generated by the vascular pulsations and is associated with the intracranial compliance, the intracranial capacity to accommodate a volume shift, which has been shown to be reduced in subjects with iNPH and idiopathic intracranial hypertension. Moreover, reduced intracranial compliance was associated with impaired glymphatic transport. Our findings suggest that the OCT parameters pBA and ONHH may be used as non-invasive predictors of elevated pulsatile ICP.

Remaining questions:

- What is the impact of reduced glymphatic clearance in the visual pathway?
- Can modulation of the glymphatic system in the visual pathway serve as a new target for treatment in glaucoma?

References

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