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INSIGHTS

The brain–eye connection: More than just action potentials

James Walsh[1]

In this issue of the *Journal of Experimental Medicine*, Cao et al. (https://doi.org/10.1084/jem.20240386) demonstrate that the connection between the eye and the brain goes beyond the impulses carried by the optic nerve and that in Alzheimer's disease (AD), the influx of toxic Aβ from the brain to the retina underlies AD-induced retinal degeneration.

It has long been known that β-amyloid (Aβ) deposition in the retina (Koronyo-Hamaoui et al., 2011) and retinal neurodegeneration (Cheung et al., 2015) are features of Alzheimer's disease (AD), yet it has been assumed that these changes were due to local production of Aβ. Until recently, the brain and the eye have been thought of as separate spaces communicating only by their neuronal connections in the optic nerve. This understanding has been evolving recently with the discovery that amyloid injected into the eye follows a glymphatic pathway to the optic nerve (Wang et al., 2020) and that immune activation in the vitreous of the eye induces immunity throughout the central nervous system (CNS) (Yin et al., 2024). Since these works showed the eye-to-brain connection, there has been an open question of whether this communication is unidirectional or if macromolecules can also travel from the brain to the eye. In this month's *Journal of Experimental Medicine*, Cao et al. (2024) tackle this question by demonstrating drainage of Aβ from the brain to the eye that could mediate this retinal degeneration in AD and examine some of the molecular correlates that influence this pathway.

The authors start by demonstrating the deposition of Aβ throughout postmortem eyes of AD patients and in the 5xFAD model of AD. In particular, they show high levels of Aβ within lymphatic vessels, in the perivascular spaces, and in the axonal tracts of the optic nerve. To determine the functional consequences of this Aβ deposition, they turned to 5xFAD mice, which have deposition of amyloid throughout the CNS. They found that these mice demonstrated retinal thinning, increased fundus autofluorescence (a measure of retinal pigment epithelium function), and a decreased ability to follow optokinetic stimuli compared with their control counterparts. Investigating the origin of the ocular Aβ, they made a key observation: two proteins vital for the production of Aβ, APP and PS1, were increased in the brains of AD patients and 5xFAD mice, yet these proteins were not differentially expressed in the retina. This led them to propose that the transport of Aβ from the brain to the eye is the key process that leads to the accumulation of Aβ in the retina. Indeed, intracisternal magna injections (into the cerebrospinal fluid, ICM) of small molecule and protein tracers led to accumulation in the periarterial spaces in the retina. Functionally, ICM injection of Aβ phenocopied many changes seen in 5xFAD mice with a decrease in retinal thickness and impaired optokinetic responses compared with vehicle injection. Anatomically, ICM injection of Aβ led to a decrease in the RPE65 and Tuj1 immunofluorescence but did not affect rhodopsin, suggesting a differential susceptibility of retinal cells to Aβ-mediated toxicity. Exploring molecular mediators of this process, they examined aquaporin 4 (Aqp4), a water channel found at high levels in astrocytes and Müller glia that plays an important role in glymphatic waste clearance in the CNS (Iliff et al., 2012). They found that mice lacking Aqp4 had greater accumulation of Aβ in the retina, greater retinal degeneration, and worsened optokinetic responses after ICM injection of Aβ, suggesting that Aqp4 is important in the clearance of Aβ from the retina.

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This work builds on the growing literature that there is a relevant connection between the eye and the brain (Yin et al., 2024; Cao et al., 2024) with far-reaching implications for neurodegenerative disease, immunity, and an array of disorders secondary to altered fluid dynamics within the

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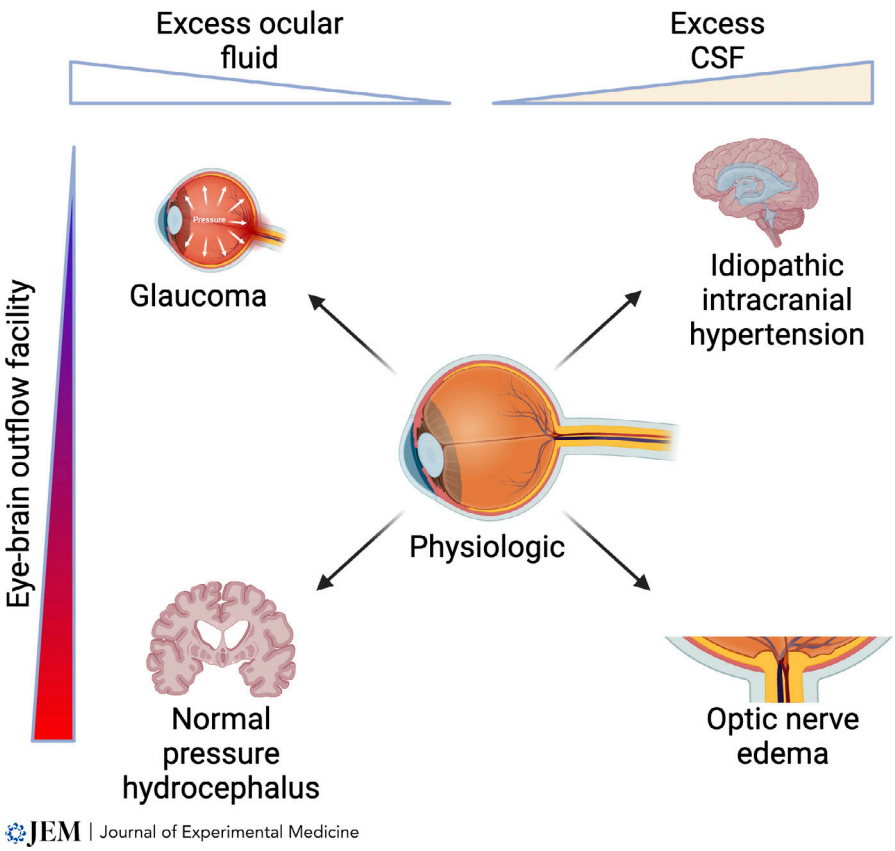

Potential disease relevance of aberrant eye–brain communication.

CNS. While the authors, as with previous works, rely primarily on injection-based models, which can be confounded by pressure changes, the authors gave additional evidence that this could be a physiologic process by demonstrating enhanced accumulation of Aβ in the retina of AD patients and in 5xFAD mice, despite similar levels of precursor and processing proteins. While the authors propose that this outflow to the eye is due to both perineural and lymphatic flow, the pathway that is dominant in the Aβ entry into the eye is unclear, which will have significant implications for how that pathway can be used to modulate disease.

Altogether, these three recent works on the communication between the eye and the brain (Cao et al., 2024; Yin et al., 2024; Wang et al., 2020) bring up a new set of questions that beg to be answered. One of the most basic questions, touched on above, is whether this sharing of macromolecules between the eye and the brain is a passive process driven by bulk fluid flow or an active process whereby specific macromolecules are selectively transported across a barrier between the eye and the brain. Our current evidence suggests that there are features of each: the applicability to multiple macromolecules and the bidirectional transport between the eye and the brain suggest that there are some non-specific features to this process, yet other experiments suggest selectivity as some macromolecules are poor substrates for this transport (Mathieu et al., 2017). Due to the breaking of physiologic barriers and the influence of injections on pressure, better models will need to be used to answer the question of what direction the flow occurs during normal physiology. Indeed, models that rely on the diffusion of tracers through intact barriers (Smyth et al., 2024) or photoconvertable fluorophores tagged on proteins (Huang et al., 2019) already exist and would be ideal for this. The final important question for understanding the mechanistic underpinnings of this process are the anatomical correlates, presumably at the optic nerve head, that are important in this process and include transport through lamina cribrorsa trabeculae, through the optic nerve sheath lymphatic vessels adjacent to the nerve, or an altogether different route.

How could these findings translate to disease processes in humans? There are many diseases in the eye and CNS that demonstrate aberrant fluid homeostasis that could potentially be influenced by a brain–eye fluid pathway (figure). For instance, the best-known disease of dysregulated fluid homeostasis in the eye is glaucoma. Aqueous outflow through the trabecular meshwork has been well-studied in the pathogenesis and therapeutic approaches for glaucoma, and the only treatments currently in use for glaucoma lower intraocular pressure (IOP) either by decreasing fluid production or by increasing outflow. However, we know that IOP is only one of the risk factors for glaucoma: some patients develop severe disease at pressures that are considered normal, while others have persistently high elevation in IOP without glaucomatous damage (Weinreb et al., 2014). While differential susceptibility of retinal ganglion cells to IOP-mediated apoptosis is frequently cited to explain this differential response to IOP, there are a host of other factors that could be contributory, such as ocular biomechanics and immunologic differences. Taking a cue from these recent studies, could it be that alteration in this eye–brain communication is one of the primary abnormalities in glaucoma? A deficit in flow across the optic nerve head could raise IOP and increase the pressure differential between the intraocular space and cerebrospinal fluid (CSF). This would put stress on the axons at the optic nerve head, which is the side of damage in glaucoma, and explain differential susceptibility to IOP and the prototypical posterior bowing of the lamina cribrosa better than current models. In this case, maybe enhancing this eye–brain communication by shunting ocular fluid into the optic nerve sheath would prove to be a more successful therapy as it could both lower IOP and alleviate the stress on the optic nerve head by equalizing the pressure differential across it.

On the other side of this connection, the brain, the authors demonstrate the relevance of this brain–eye communication in neurodegenerative disease but leave us to speculate on other pathologies in which this process could be relevant. Previous clinical case reports have reported that intraocular silicone oil can migrate to the lateral ventricles

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(Cao et al., 2019), suggesting that there is a specific connection between the intraocular space and the ventricles. In normal pressure hydrocephalus (NPH), there is ventriculomegaly without an increase in intracranial pressure: could it be that there is enhanced drainage through from the eye that leads to local pressure gradients in the ventricles? Therefore, it is conceivable that NPH is a disease of increased fluid flow from the eye to the brain, and inhibiting this pathway could prove to be safer and more effective than ventriculoperitoneal shunting, which is currently the mainstay of therapy. Along a similar line of reasoning, then, could idiopathic intracranial hypertension, which is characterized by high intracranial pressure and optic nerve edema, be due to poor fluid communication between the CSF and intraocular space?

Finally, the flow of macromolecules is particularly relevant in adaptive immunity, where peptidergic communication generates the antigenic cues that underlie immune activation. While the adaptive immune system has classically been thought to be dampened in the eye and the brain, we have known for a long time that CNS inflammation is linked to ocular inflammation (Ness et al., 2017; Budoff et al., 2019), and we are beginning to understand more and more how the adaptive immune system can support the functioning of the CNS (Walsh et al., 2015; Derecki et al., 2010). Whether this brain–eye communication can be leveraged to enhance shared protection from pathogens, to augment physiological tissue functioning, and to provide a minimally invasive method to diagnose neurologic disease will remain to be seen.

In summary, there are many situations where communication between the eye and the brain could prove to be relevant, and as we explore how the brain and the eye interact with each other, we should continue to think of how this goes beyond the electrical impulses carried on the optic nerve.

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