Dynamics between cerebrospinal fluid and aqueous humour – are they bidirectional?

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Abstract

The ophthalmology examination is crucial for the treatment of certain systemic diseases. The eye is an anatomical extension of the brain, and many similarities can be found between them. Multidisciplinary research of the brain or the eye will cross-fertilise each other, especially in the context of neurodegenerative diseases. As an extension of the telencephalon, the optic nerve is surrounded by the meninges and cerebrospinal fluid, just like the brain. Numerous studies and hypotheses have focused on the movement of cerebrospinal fluid in this region, particularly the influence of pressure on this area and the translaminar pressure gradient that develops as a result of this pressure. In the 1970s, Volkov proposed the theory that glaucoma is a two-pressure disease, which was supported by studies on astronauts, who often exhibit visual disturbances with swelling of the eye disc. Understanding the balance between intraocular pressure, cerebrospinal fluid pressure, and systemic blood pressure is key to better management of diseases such as glaucoma and intracranial hypertension. The aim of this article was to re-evaluate the current state of knowledge in order to improve the treatment of pathological conditions resulting from disturbances in aqueous humour and cerebrospinal fluid flow.

Key words: *CSF dynamics; eye; glaucoma; lamina cribrosa; optic nerve*

Introduction

The use of the eye as a window into changes in the brain is rapidly increasing in research. The results of these studies impact both the understanding of the effects of neurological diseases on vision and the possibility of using eye tests to detect or monitor systemic diseases. In addition, the eye is the only place in the body where both neurons and blood vessels can be seen directly. Therefore, eye examination is a routine part of the treatment of vascular diseases such as diabetes and hypertension.

For many professionals, it is difficult to determine whether visual symptoms are caused by a brain disease or an eye condition. A better understanding of the visual signs of neurodegenerative diseases will help to treat patients more effectively. While further research is needed to understand the dynamics of aqueous humour and cerebrospinal fluid and their

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role in the development of certain diseases, this paper aims to reassess the current state of knowledge in order to improve treatment of pathological conditions resulting from disturbances in the flow of these two fluids.

Aqueous humour dynamics

The aqueous humour (AH) is a clear, colourless fluid containing electrolytes, glucose, amino acids and ascorbic acid. It not only fills the anterior and posterior chambers of the eye, but also nourishes avascular structures such as the cornea and lens (König and Liebich, 2009) and removes metabolic waste while maintaining intraocular pressure (IOP) (Pizzirani and Gong, 2015). It is secreted from the non-pigmented epithelium of the ciliary body by diffusion, ultrafiltration and active secretion (Maggio, 2015). The production process begins with the diffusion of plasma through the fenestrated endothelium of the blood vessels in the vascular stroma of the ciliary body, while ultrafiltration allows the passage of molecules along osmotic gradients. In contrast to diffusion and ultrafiltration, active secretion requires energy, which is promoted by carbonic anhydrase and adenosine triphosphate in the non-pigmented epithelium (Pizzirani and Gong, 2015).

Drainage of AH occurs via two complex hydraulic systems: the anterior (trabecular or conventional) and posterior (uveoscleral or unconventional) outflow pathways, which provide a constant outflow of AH and help to maintain physiologic IOP with continuous production. The conventional pathway handles most of the outflow, with AH flowing from the posterior to the anterior chamber of the eye, crossing the iridocorneal angle (Brooks, 1990) and entering the trabecular meshwork (TM) via the ciliary canal. From there, AH moves through endothelial cells and forms large intracellular vacuoles that eventually drain into the systemic circulation (Pizzirani and Gong, 2015). The unconventional pathway drains the portion of the AH that bypasses the trabecular meshwork, collects in the uveoscleral space, and flows through the posterior uveoscleral region. This type of drainage is passive and independent of the IOP, and in dogs for example, accounts for approximately 15% of AH outflow.

The balance between AH production and drainage results in a relatively stable IOP, which is influenced by factors such as age, species, mean arterial pressure, central venous pressure, blood osmolality and episcleral venous pressure. IOP is critical for maintaining the shape of the eye and ensuring tight adhesion between the retina and choroid. Disturbances in AH outflow can lead to an increase in IOP, resulting in retinal atrophy and eventually blindness (König and Liebich, 2009).

Most previous research has focused on studying the movement of AH in the anterior segment of the eye, while much less is known about the outflow in the posterior chamber. This could be because the vitreous, which has a fixed and stable volume, is not involved in the circulation of AH and prevents its movement towards the posterior segment (Mathieu et al., 2017). In addition, the retina and optic nerve (ON) are supplied with nutrients via blood vessels, so such circulation is not necessary (Mathieu et al., 2017). However, some studies have indicated the possibility of posterior AH flow. An important indicator of potential posterior AH flow is the origin of the fluid component of the vitreous (Davson, 1962; Toris, 2008). It has been demonstrated that after removal of the ciliary processes in rabbits, AH production ceases completely, resulting in vitreous atrophy, supporting the hypothesis that

Table 1. Composition difference between plasma, aqueous humour and cerebrospinal fluid (Modified from: Hayashy et al, 2016; Fogh et al., 2020)

Component	Plasma (mmol/L)	Aqueous humor (mmol/L)	Cerebrospinal fluid (mmol/L)
$HCO3^-$	26	22	21
Ca2+	4.9	2.5	2.3
Cl^-	107	131	130
Glucose	5.9	2.8	6
Lactate	1.9	2.8	1.6
Mg_2^+	1.2	1.2	1.7
PO_4^{3-}	1.1	0.5	0.6
K^+	4.6	2.2	2.9
Na^+	148	152	147
Urea	7.3	6.1	7
Protein (mg/dL)	7000	24	35
pH	7.4	7.2	7.3

AH serves as the source of vitreous fluid (Hayreh, 1969; Mathieu et al., 2017). Other studies confirmed this posterior flow of AH in monkeys, suggesting that the fluid is transported across the retinal pigment epithelium where it is then reabsorbed by the choroid (Cantrill and Pederson, 1982; Toris and Pederson, 1985).

In addition to posterior flow from the vitreous to the retina, studies in rabbits and dogs have demonstrated posterior movement of solutes from the vitreous into the ON with various chemical tracers (Rodriguez-Peralta, 1966; Hayreh, 1978). The presence of posterior AH flow could be important for several reasons. First, this flow could provide an additional outflow pathway for AH, which is particularly important when anterior outflow is compromised (Mathieu et al., 2017). Since there are no conventional lymphatic vessels in the retina and ON, the continuous flow of fluid through these structures could help remove dissolved substances and metabolic products and maintain interstitial fluid homeostasis – an essential factor for normal cell and tissue function.

Cerebrospinal fluid dynamics

Cerebrospinal fluid (CSF) is a clear fluid that surrounds the central nervous system to ensure the supply of nutrients and facilitate the removal of metabolic waste (Kapoor et al., 2008; Mathieu et al., 2018). The CSF is mainly composed of water (99%) (Table 1) and fills the subarachnoid spaces, perivascular spaces and cerebral ventricles within the central nervous system, including the spaces in the brain, spinal cord and ON (Khasawneh et al., 2018; Sheng et al., 2022). The CSF also fills the subarachnoid space surrounding the optic nerve (ONSAS), which surrounds the retrolaminar portion of the ON behind the eye and ends at the sclera. Morphologically, the ONSAS forms a cul-de-sac. For CSF to be exchanged between the cranial cavity and the ONSAS, it must exit the same way it entered (Killer et al., 2003).

Although numerous studies and hypotheses have investigated CSF movement in this region, detailed information about the circulation patterns of CSF around the ON is still largely unknown.

Cerebrospinal fluid is primarily produced in the choroid plexus of the brain and then distributed through the ventricles and around the neural tissue (Jonas et al., 2003). Drainage of CSF through dural lymphatics and arachnoid granulations into the venous system balances its production and presumably contributes to the regulation of pressure in the ONSAS (Kapoor et al., 2008; Mathieu et al., 2017). The cranial subarachnoid space is connected to the ONSAS.

Beyond the eye – the brain connection

The eye is an anatomical extension of the brain. Therefore, many parallels can be drawn between these two organs, particularly in terms of their neurons, vasculature and immune response. As both organs change in similar ways due to disease, multidisciplinary research investigating each organ will cross-fertilize the other, especially in the context of neurodegenerative diseases.

The optic nerve enters the intracranial space through the optic canal. Its length varies between 42 and 47 mm (Hayreh, 2011). Structurally, it can be divided into four sections: the intraocular, intraorbital, intracanalicular and intracranial (Killer, 2003).

The intraorbital section of the ON is surrounded by the meninges, which consist of three layers: dura mater, arachnoid mater and pia mater. In this section, the ON takes on a slight S-shape (Salazar et al., 2019). The width of the subarachnoid space in this region narrows from the retrobulbar portion to the intracanalicular portion. The diameter of this nerve section in humans is between 5.17±1.34 mm and 3.55±0.82 mm and can be used to assess cerebrospinal fluid pressure (CSFP) (Killer et al., 2011).

As an extension of the telencephalon, the optic nerve, like the brain, is surrounded by CSF. The subarachnoid space of the ON forms a microenvironment for the ON. This space is not empty but is filled with a complex network of trabeculae and septa covered by layers of meningothelial cells. The subarachnoid space of the optic nerve is partially connected to the intracranial subarachnoid space, with this connection ending at the junction between the nerve and the eyeball. At this junction lies the lamina cribrosa, a connective tissue structure that is considered by many authors to be a barrier that prevents the CSFP from affecting the eye (Wostyn et al., 2016). The IOP is exerted anterior to the lamina cribrosa, inside the eye. Posteriorly, the orbital part of the ON is surrounded by CSF in the intracranial subarachnoid space. This creates a separation between the higher-pressure eyeball and the lower pressure retrobulbar space, resulting in a translaminar pressure gradient (TLG) through the lamina cribrosa (Balaratnasingam et al., 2009).

Due to the volume gradient between the intracranial space and the ONSAS, a unidirectional CSF flow from the intracranial space to the ON is generally expected (Liu et al., 2021; Sheng et al., 2022). However, the CSF can flow back into the intracranial space if the pressure in the ONSAS exceeds that of the intracranial space. According to Golzan et al. (2012), CSF pulsation corresponds to arterial flow in the ON, while reflexive CSF flow, which refers to backflow from the lamina cribrosa, corresponds to venous flow. This phenomenon suggests that the pulsations of blood flow act as a driving force for the

movement of CSF in the ON. Morgan et al. (1998) found that pressure in the retrolaminar region is not always directly related to intracranial CSF pressure, suggesting that CSF flow in the ON is not consistently related to arterial pulsation. These results suggest that CSF in ON likely has a unique driving force that is independent of intracranial blood flow (Boye et al., 2018).

Given the crucial role of the CSF, it is not surprising that disturbances in its dynamics are associated with a number of central nervous system disorders that affect both the brain and the ON, such as idiopathic intracranial hypertension (IIH), papilledema, hydrocephalus, normal tension glaucoma (NTG), and possibly congenital glaucoma (Simon, 2016). Detailed information about CSF dynamics in the ONSAS could enhance understanding of these diseases, as well as neuro-ocular disorders linked to spaceflight-associated neuro-ocular syndrome (SANS) (Simon, 2016; Bothwell et al., 2019; Wang et al., 2023).

Glaucoma: a two-pressure disease?

In the 1970s, Volkov proposed the theory of glaucoma as a two-pressure disease, a concept that was later expanded by Berdahl (2008) and most recently by Hoang et al. (2024). They investigated whether abnormal pressure outside the eye could cause normal tension glaucoma (NTG). NTG is a condition in which the IOP is normal while the CSFP level is lower than normal (Siaudvytyte et al., 2016; Stoskuviene et al., 2023). Glaucoma patients experience visual field loss and optic disc excavation identical to primary open-angle glaucoma (POAG) despite apparently normal intraocular pressure. Initially, NTG was associated with vascular deregulation leading to impaired blood flow to the optic nerve head (ONH). Later, a new hypothesis involving the CSFP factor was formulated. A relatively low CSFP may produce mechanical conditions that act on the ONH like a relatively elevated IOP.

This theory has been supported by studies on astronauts, who often exhibit visual disturbances with disc swelling (Zhang and Hargens, 2017). After six months of spaceflight, astronauts often develop a clinical syndrome SANS, which has clear similarities to IIH with papilledema (Mader et al., 2011). This phenotype is explained by the lack of gravity, which allows CSF to diffuse equally through the intracranial subarachnoid space, leading to increased venous pressure and a higher CSFP at the eye (Kramer et al., 2012; Mirra et al., 2020).

Glaucoma is a heterogeneous group of progressive diseases (Pizzirani and Gong, 2015) characterised by increased IOP and subsequent vision loss (Miller, 2008). It is often misdiagnosed as an eye disease and is one of the leading causes of blindness in middle-aged dogs (Hamor, 2014). Increased IOP leads to pathological changes in the optic disc and visual field defects. The underlying cause of glaucoma is impaired AH drainage (Tinsley and Betts, 1993), and the resulting damage to eye tissue is similar for different causes. As IOP is no longer considered the primary indicator of glaucoma, attention should be focused on damage to the ON and surrounding structures. Glaucoma is a multifactorial disease with different phenotypes and aetiologies.

Numerous risk factors have been associated with the development of glaucoma and some may be related to CSFP. These factors may influence CSFP as a potential risk factor for glaucoma. In general, a positive correlation has been found between glaucoma and increased body mass index

(BMI), especially in women (Ren et al., 2012). Age is an equally well-documented risk factor for glaucoma. Although some earlier studies investigating CSFP and age found no correlation (Mirra et al., 2020), a more recent study provided some evidence of a link between CSFP and age. CSFP decreased progressively in the 6th decade of life. Interestingly, the age at which CSFP begins to decline coincides with the age at which the prevalence of POAG increases (Fleischman et al. 2012).

Conclusion

To summarise, ONH health depends on the balance between IOP, CSFP and mean arterial blood pressure. Therefore, the contribution of research in this area is important to our further understanding of the homeostatic mechanisms that maintain the integrity of ONH morphology during acute pressure changes. These studies may contribute to a better understanding of the pathogenesis and treatment of IIH, glaucoma and other diseases of the ONH.

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Dinamika između cerebrospinalne tekućine i očne vodice – je li dvosmjerna?

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Oftalmološki pregled ključan je za dijagnostiku i praćenje nekih sistemskih bolesti. Štoviše, s obzirom na to da je oko anatomski produžetak mozga, mogu se povući brojne sličnosti između ova dva organa. Puno multidisciplinarnih istraživanja koja proučavaju oba područja međusobno se nadopunjavaju, posebice u kontekstu neurodegenerativnih bolesti. Kao produžetak telencefalona, očni živac okružen je moždanim ovojnicama i cerebrospinalnom tekućinom, baš kao i mozak. Brojna istraživanja proučavaju kretanje cerebrospinalne tekućine u području očnog živca, posebno utjecaj tlakova na to područje i razvoj translaminarnog gradijenta tlaka (TLG) koji nastaje kao rezultat tih tlakova. Volkov je 1970-ih predložio teoriju da je glaukom bolest dvaju tlakova, a tu teoriju su podržala istraživanja provedena na astronautima, koji često doživljavaju smetnje vida i edem očnog živca (engl. *Spaceflight-Associated Neuro-Ocular Syndrome, SANS*). Razumijevanje ravnoteže između očnog tlaka (IOP), cerebrospinalnog tlaka (CSFP) i krvnog tlaka ključno je za bolju kontrolu bolesti poput glaukoma i intrakranijalne hipertenzije. Iako su potrebna dodatna istraživanja u svrhu određivanja dinamike očne vodice i cerebrospinalnog likvora kao i posljedičnog nastanka određenih bolesti, cilj ovog rada je bio analizirati dosadašnje spoznaje da bi se poboljšalo liječenje određenih patoloških stanja nastalih posljedično poremećaju dinamike ovih tekućina.

Ključne riječi: *dinamika cerebrospinalne tekućine, oko, glaukom, lamina cribrosa, očni živac*