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An hypothesis on pressure transmission from anterior chamber to optic nerve*

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Abstract

Few studies have characterized how pressure in the anterior chamber (AC) of the eye is transmitted via the vitreous to the vitreous–ganglion cell interface. We are aware of only one study that simultaneously measured the pressures in the AC and vitreous humor; and of only one study that simultaneously measured the pressures in the AC and the suprachoroidal space (SCS). The pressure in the AC is defined as the intraocular pressure (IOP), which when elevated beyond statistically normal limits is a recognized risk factor for glaucoma, a malady best described as an optic neuropathy with degeneration and eventual death of the retinal ganglion cells (GC's) and highly characteristic changes in the optic nerve head (ONH). Most investigators currently believe that the prevalent risk factor for GC apoptosis is ocular hypertension, but no one has demonstrated how an increase in IOP in the AC is transmitted to the GC's. In patients with primary open angle glaucoma, the pressure in the AC increases due to an increase in the resistance of the trabecular meshwork (TM) outflow pathway. We questioned how such increased pressure in the AC would be transmitted to the GC to produce the changes in the ONH seen in glaucoma. Based on our preliminary data and purview of the literature, we hypothesize that a pressure increase originating in the AC is likely transmitted via both the SCS and the vitreous, with transmission via the former pathway probably most efficient in affecting the GC. Independently of the mechanism that produces GC apoptosis, the ones that are first affected, as repeatedly shown by visual field tests, are the most peripheral ones; i.e., those whose axons are the most external as they form the ONH and enter the lamina cribrosa. There are no published reports explaining this peculiarity. The dogma is that the pressure transmitted via the vitreous is higher at the periphery because it is transmitted across a shorter distance, since the vitreous acts as a buffer that absorbs part of the pressure being transmitted. We propose that IOP is not only transmitted via the vitreous but also via the SCS. Increases in IOP could be efficiently applied via the SCS to the most external axons of the ONH as they leave the eye. Our hypothesis can also explain low-tension glaucoma in which

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Conflicts of interest

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the most peripheral GC's are also affected first, because pressure is transmitted without decay due to a reduced uveoscleral (UVS) flow.

Introduction

Primary open angle glaucoma (POAG) is an optic neuropathy that is commonly associated with increased intraocular pressure (IOP). High IOP leads to retinal ganglion cell (GC) death and typical cupping of the optic disk [1]. During the last decade IOP has been confirmed as one of the risk factors for development and progression of glaucoma in various multicenter trials (OHTS, AGIS, and EMGT) [2–4].

Although an alternative approach to treatment of glaucoma based on “neuroprotection” (using treatments that prevent death of the retinal ganglion cells) has been tried, it has to date remained unsuccessful (Memantine trial) [5]. Thus, IOP lowering remains the only modality to treat glaucoma, even when IOP is within the “normal” range [6].

To our knowledge, no study has clearly defined how the IOP, which is usually measured trans-corneally as the anterior chamber pressure (ACP) is applied to the retina.

The underlying assumption is that it is transmitted via the vitreous humor and applied perpendicularly to the retinal surface where the GC's reside. This presumption has been disseminated by various figures in the ophthalmic literature showing arrows applied perpendicular to the whole retina to represent the IOP. However, the actual magnitude of the pressure applied to the GC has not been directly measured. This would require the implementation of minute pressure detectors at the vitreous–retina interface.

This measurement has never been implemented, nevertheless, it is a dogma among glaucoma clinicians and researchers that this is the manner by which IOP affects the GC's, whose axons send the visual information.

Many factors that could be responsible for the death of the GC including retinal ischemia due to reduced ocular perfusion, neurotrophin deprivation, induction of apoptotic cascades, etc. have been proposed [7,8], but independently of the mechanism that produces the death of the GC, the ones that are first affected, as repeatedly shown by visual field tests, are the most peripheral ones; i.e., those whose axons are the most external as they form the optic nerve (ON) and enter the lamina cribrosa.

There are no published reports explaining this peculiarity. Again, the dogma is that the pressure transmitted via the vitreous is higher at the periphery because it is transmitted across a shorter distance, since the vitreous acts as a buffer that absorbs part of the pressure being transmitted. However, without treatment, the same pressure that initially only affects the peripheral GC, with time, also affects the less peripheral ones in an orderly fashion. No experimental explanation has been advanced for this particular progression of the disease.

Hypothesis

We propose that ACP is not only transmitted via the vitreous but also via the supraciliary (Sci) and suprachoroidal spaces (SCSs). This virtual space has been utilized to deliver medications to the retina from the anterior segment near the ciliary body [9,10]. Thus, IOP could be applied to the retina via the vitreous but also around the most external axons of the optic nerve head (ONH) as they leave the eye via the SCS.

Our hypothesis could:

- A. Explain why the most peripheral GC's are affected first;
- B. explain low-tension glaucoma in which the most peripheral GC's are also affected first; and
- C. provide a plausible series of experimental tests; unlike the placement of pressure detectors in the vitreous-retina interface, which is currently technically difficult.

Interpretation of the hypothesis

- A. The communication between the AC and the Sci and the SCS allows for a flow and pressure transmission all the way to the end of the SCS which surrounds the confluent axons of the GC to form the ON. This space is part of the uveoscleral (UVS) pathway that serves as a parallel path for aqueous humor outflow. The anatomy and physiology of the UVS pathway has been described in detail in several animals, especially in monkey by Anders Bill [11], who has been credited with its discovery. More recently, Pederson provided a particularly didactic presentation on the UVS pathway [12]. AH flowthrough this space to leave the eye via the sclera and emissarial channels. Because of this flow, pressure drops along the way, but there is a residual pressure at the end of the UVS path which is applied to the most external de-myelinated axons of the ON. These axons correspond to the more peripheral GC's. This idea with possible flows and pressures is represented with a schematic two-dimensional model in Fig. 1. IOP in the AC is assumed to be 16 mmHg. Flow (F_t) via the trabecular meshwork (TM) is $2.4 \mu\text{l/min}$, whereas, F_u via the UVS path is $0.4 \mu\text{l/min}$. The facilities of the outflows, or outflow conductances (C) of the TM, and of the UVS pathway between points 1 and 2, are 0.3 and $0.067 \mu\text{l/min/mmHg}$, respectively. The pressure drop between the AC and the last emissarial channel (represented as a single one) is $F_u/C_u \approx 6 \text{ mmHg}$. Thus, the pressure on the last portion of the SCS that is applied to the axons is $16 - 6$, or 10 mmHg. This could be the pressure that the axons can tolerate without damage. Without a detailed analysis of all possible changes, it is obvious that the larger the F_u , the smaller the pressure at the dead end of the SCS. Also, with all other parameters constant, the larger the IOP, the larger the pressure at the end of the SCS. For example, if IOP increases to 20 mmHg due to diminished drainage of the TM, the pressure at the end of the SCS could rise from 10 to about 14 mmHg, if the facility and flow via the UVP remain the same. This higher pressure at the end of the SCS could be deleterious, and we propose that it is the excessive pressure applied to the axons of the peripheral GC's that induces the death of the corresponding GC's. As the external axons die, the pressure is exerted on the layer below, in turn affecting their signal transmission with the consequent death of the GC's.
- B. We propose that in low-tension glaucoma, there is a considerable reduction in the facility of the UVS path and thus a reduction of the UVS flow. Without this flow, the 16 mmHg IOP in the AC will be transmitted to the end of the SCS without decline. This pressure will be larger than the lower pressure normally tolerated by the axons. The progression of the disease will be the same as in POAG. In the case of individuals with a loss of visual field, who have an IOP within normal limits, current therapeutic modalities include IOP reduction to slow the progression of visual field loss [13,14]. It has also been determined that the treatment of choice is the administration of prostanoids, which increase UVS outflow and thus produce a drop in the pressure transmitted to the axons.
- C. It is technically feasible to place pressure detectors in the SCS and monitor the transmission of pressure between the AC and the far end of the SCS. We are

presenting preliminary data indicating that this measurement is possible using the isolated bovine eye, in support of our hypothesis.

Evaluation of the hypothesis

The best previous evidence supporting our hypothesis is the work by Pederson and the references in his chapter “uveoscleral outflow” [12]. He describes the Sci and SCS, their physiology, pressure transmission, fluid flow, and decreasing pressure gradient as AH flows away from the AC, but he stops short of suggesting that the pressure at the end of the SCS could affect the axons of the ON at that level. This unrecognized possibility is the heart of our hypothesis.

Empirical data

Most of the work reviewed by Pederson was done in monkey. We decided to test our hypothesis with additional preliminary experiments in the isolated bovine eye. Following, the methodology and results are described. The eyes were transferred on ice from the slaughterhouse to our laboratory in the city of Corrientes, Argentina. A 2-mm sclera flap was opened posterior to the eye’s equator near the optic nerve (at about 5–7 mm from it) and the tip of a 27-ga needle was placed under the flap, which was closed and sealed with cyanoacrylate adhesive glue. As such, this needle resided between the external sclera coat of the eyeball and the choroid, hence within the SCS. The needle was connected with polyethylene tubing to a graduated pipette filled with physiological saline up to a given level. The AC was punctured with another needle connected to a syringe and to a pressure transducer (model MPVZ 50106, Freescale Semiconductor, Austin, TX), the output of which was read by a calibrated digital voltmeter. Thus, the pressure in the AC was directly measured with the meter and could be changed by injecting or withdrawing fluid with the syringe. The pressure in the SCS could be regulated by moving the pipette vertically, and determined by the height of the column of fluid with respect to the position of the AC. This method is illustrated in Fig. 2. The inside of the pipette was pretreated with a hydrophobic agent (Rain-X; SOAPUS Products, Houston, TX) to prevent meniscus crawl and enable that the height of fluid within the pipette be determined accurately. The level of fluid in the open pipette was set to coincide with the pressure (IOP) in the AC. Then, the pipette was moved vertically to determine if this change in pressure in the SCS was transmitted to the AC. Initially, IOP was maintained at ≈ 15 mmHg by injecting small amounts of fluid into the AC to compensate for spontaneous leaks in the isolated eyes. The rate of such fluid compensation was about 3–5 $\mu\text{l}/\text{min}$.

Table 1 shows the results of 11 experiments. Initially, the pressure in the AC was stabilized to about 15 mmHg and the fluid level of the pipette was set to 14.71 mmHg, a stable value similar to that in the AC. Then, the level in the pipette was sequentially increased to 22.06 and 29.41 mmHg. The measured pressure in the AC reacted within 5 s and remained stable at smaller values of 18.86 and 23.80 mmHg, respectively, for at least 5 min. This difference in pressure (22.06–18.86, or 29.41–23.80) suggested a flow from pipette via SCS to AC. Following this, the fluid level in the pipette was lowered in steps to 14.71, 7.35, and 3.68 mmHg. Simultaneously, the IOP in the AC stabilized at 15.80, 12.86, and 11.07 mmHg, respectively, which are values higher than in the SCS suggesting a reversal of flow, now in the AC-to-SCS direction. Then AC pressure and pipette level were set to the initial control values (Table 1, bottom rows) and after 5 min of stabilization, the entire protocol was repeated. The results of the second run were the same as those of the first run. The values in Table 1 are plotted in Fig. 3 to visualize the relation between the AC and SCS pressures. It clearly shows the crossover point at about 15 mmHg.

Discussion

We present results of pressure transmission between the AC and the SCS in the isolated cow eye to support our hypothesis that the IOP can be transmitted to the axons of the peripheral GC's via the UVS pathway. Table 1 shows the reproducibility of the results by comparing the top and bottom part of the table for the same pressure. Depending on the pressure difference between SCS and AC, a fluid movement in either direction can be inferred. It is interesting to note that a crossover point in Fig. 3 is about 15 mmHg. This point represents a change in direction of fluid movement between the two compartments, indicating an open communication as previously reported by Emi, Pederson, and Toris [15].

We are also aware of data indicating hydrodynamic communication between the vitreous humor and the AC in isolated cow eyes [16], and that the vitreous body of the cow eye may be more firm than that of the adult human eye [16], which raises the possibility that species with a less gelatinous vitreous humor may exhibit a greater capacity for pressure transmission by the vitreous body. Nevertheless, a pressure transmission via the SCS is clearly evident.

To the best of our knowledge, no investigators have demonstrated a pressure transmission from the AC to the vitreous in a live animal. We are aware of only one study that reported the simultaneous measurements of the pressures in the AC and vitreous body upon increasing the pressure in the AC, and this work was done in isolated porcine eyes [17]. This study demonstrated that rapidly increasing the pressure of the AC to a steady value of 135 mmHg (by inserting a cannula connected to a water column into the AC) resulted in a steady-state value of 55 mmHg in the vitreous cavity, thereby indicating that the pressure change in the latter compartment was markedly less than that of the former [17].

Regarding pressure transmission between the AC and SCS, Emi, Pederson, and Toris measured the hydrostatic pressure of the supraciliary space and the posterior suprachoroidal space in the eyes of live monkeys [15]. They reported that the pressures of these compartments were consistently lower than the IOP (i.e., the ACP), which they adjusted to various levels between 5 and 60 mmHg. In their data, the pressure difference between the AC and the posterior suprachoroidal space increased with higher levels of IOP. In the control eye with a spontaneous (i.e., unadjusted) IOP of about 9 mmHg, the pressure in the posterior suprachoroidal space was 3.5 mmHg lower. This pressure difference increased to about 10 mmHg when IOP was elevated to 60 mmHg [15]. They also presented evidence that this hydrostatic pressure difference is generated primarily by the colloid osmotic absorption of the choroidal vessels, as well as, a contribution from the outflow of fluid across the sclera and emissarial pores.

In contrast to these *in vivo* results, under our conditions with the isolated bovine eyes there would be no steady-state blood flow in the choroidal vessels. As aforementioned, we purposely set the pressure in the SCS either higher or lower to show that the transmission was bi-directional, at least in the isolated cow eye. Pressure in the AC higher than the SCS established a flow in the direction that would occur in the *in vivo* eye; whereas, when pressure in the AC was lower than SCS, a flow is induced opposite that of the normal physiological situation *in vivo* [12,18].

Interestingly, Emi et al. [15] increased the IOP in the living monkey eye by infusing fluid into the vitreous cavity. Such infusions resulted in pressure elevations that were measured in the AC and posterior SCS. Thus, when pressure is directly applied to the vitreous, it can be transmitted to the AC and SCS. However, this is not the manner by which IOP increases in POAG. In patients with ocular hypertension, the pressure in the AC increases due to an increase in the resistance of the TM outflow pathway. We questioned how such increased

pressure in the AC would be transmitted to the GC to produce the changes in the ONH seen in glaucoma. Based on our hypothesis, a pressure increase originating in the AC is likely transmitted via both the SCS and the vitreous, with transmission via the former pathway probably more efficient in affecting the GC. In this regard, we would like to point out that Coleman [19], who simultaneously monitored the pressures in the AC and vitreous of live monkeys upon stimulating the ciliary muscle electrically, did not obtain evidence consistent with a transmission of pressure from the AC to the vitreous.

We suggest that pressure applied around the axons leaving the eye, as they come in contact with the SCS, is lower than in the AC. This is due to the pressure drop resulting from the flow in the SCS as AH leaves the eye via the UVS pathway. If the UVS pathway were not functional, the SCS would resemble a dead-end space and the pressure in the AC would be transmitted in its entirety around the optic nerve. In such case, the pressure in the AC could be “normal”, but that around the optic nerve would be relatively higher, potentially creating “normal tension glaucoma”. This type of glaucoma can be treated with prostanoids, which re-establish a UVS outflow.

In short, our hypothesis can be summarized as follows. Aqueous humor is constantly reaching the AC and drained via the TM and UVS pathways [11,12,18]. In the latter pathway, as fluid moves under the sclera and leaves the eye, the pressure drops and the pressure exerted in the most posterior part of the sclera will be lower than that in the AC. How much lower depends on the relative resistance between the TM and the UVS pathways and the flow across each pathway. The higher the UVS flow, the less the pressure around the optic nerve compared to the pressure in the AC. If there were no flow in the SCS, pressure in the AC would be transmitted unmitigated to the ONH potentially causing axonal loss. The rate of flow in the SCS would determine the fraction of IOP applied to the ONH.

In summary, increased pressure in the AC, classically determined as the IOP, can be transmitted to the GC via two pathways – transmission by the vitreous to the cell body of the GC, and by the SCS to the axons of the GC as they leave the eye. In both cases, the peripheral GC will be more affected because they are closer to the AC and a smaller pressure drop across the vitreous is expected, and because the axons of the peripheral GC are the most external in the optic nerve as it leaves the eye.

Based on our hypothesis, approaches to increase flow via the SCS in those with normal tension glaucoma should prove therapeutically advantageous. Moreover, our hypothesis can be directly tested in live animal models with present day methodologies.

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Fig. 1.

Two-dimensional schematic model to indicate pressure drop between the AC and end of the uveoscleral pathway (UVP). Values are assumed based on publications. C_{TM} is the hydraulic conductance or facility of the trabecular meshwork (TM). Fluid exit via emissarial channels (Ems Ch) plus possible fluid absorption by the choroidal vasculature is represented by a single output labeled “2”. No further outflows are assumed between points 2 and 3, so that pressure is the same at those points. At point 1, IOP is 16 mmHg. Pressure at episcleral veins is 8 mmHg. Outflow via the TM = $(16 - 8) * 0.3 = 2.4 \mu\text{l}/\text{min}$. The facility in the UVP between points 1 and 2 is $0.067 \mu\text{l}/\text{min}/\text{mmHg}$. Flow via UVP is $0.4 \mu\text{l}/\text{min}$. At point 2, pressure is 16 mmHg minus $(0.4/0.067) = 10 \text{ mmHg}$.

Fig. 2.

Experimental setup to measure pressure communication between the AC and posterior area of the SCS in isolated bovine eyes. A schematic diagram of the setup is shown with the SCS exaggerated for didactic purposes. The needle in the SCS was connected to the pipette with small tubing filled with fluid. The AC was punctured with a second needle connected to a syringe and a digital pressure detector. In the *in situ* eye, AH drains from the AC via the trabecular meshwork (TM) and the SCS communicating with the uveoscleral (UVS) pathway. As fluid circulates from the anterior to the posterior part of the eye under the sclera to leave the eye, the pressure in the SCS drops so that the pressure around the ON head (ONP) is lower than the IOP determined in the AC. In the absence of this circulation IOP

should be equal to ONP. If we artificially inject fluid in the posterior part of the SCS so that ONP becomes larger than IOP, fluid will circulate in the opposite direction.

Fig. 3.
A plot of the values shown in Table 1.

Experiments demonstrating transmission of pressure between the suprachoroidal space (SCS) and the anterior chamber (AC) in isolated bovine eyes.

Table 1

Pipette column of water (cm)	Pressure in the SCS (mmHg)	AC response (mmHg)		Time (min)
		Mean (n = 11)	SE	
20	14.71	15.20	0.30	5
30	22.06 →	18.86	0.67	5
40	29.41 →	23.80	0.89	5
20	14.71	15.80	0.64	5
10	7.35 ←	12.86	0.63	5
5	3.68 ←	11.07	0.66	5
30	22.06 →	17.77	0.85	5
40	29.41 →	23.26	0.92	5
20	14.71	15.20	0.56	5
10	7.35 ←	11.93	0.49	5
5	3.68 ←	10.25	0.53	5

The AC pressure response to the induced pressure in the SCS was allowed to remain stable for at least 5 min before the pressure in the SCS was adjusted to the next level/value. Arrows indicate the presumed direction of flow. First 6 rows of values within the table are from the first run of the protocol, which was immediately repeated on the same eyes to determine the reproducibility of the responses of the pressures in the AC compartment.