Roles of the ocular pressure, pressure-sensitive ion channel, and elasticity in pressure-induced retinal diseases

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Abstract

The intraocular pressure inside the human eye maintains 10–21 mmHg above the atmospheric pressure. Elevation of intraocular pressure is highly correlated with the retinopathy in glaucoma, and changes in the exterior pressure during mountain hiking, air traveling, and diving may also induce vision decline and retinopathy. The pathophysiological mechanism of these pressure-induced retinal disorders has not been completely clear. Retinal neurons express pressure-sensitive channels intrinsically sensitive to pressure and membrane stretch, such as the transient receptor potential channel (TRP) family permeable to Ca\(^{2+}\) and Na\(^{+}\) and the two-pore domain K channel family. Recent data have shown that pressure excites the primate retinal bipolar cell by opening TRP vanilloid 4 to mediate transient depolarizing currents, and TRP vanilloid 4 agonists enhance the membrane excitability of primate retinal ganglion cells. The eyeball wall is constructed primarily by the sclera and cornea of low elasticity, and the flow rate of the aqueous humor and intraocular pressure both fluctuate, but the mathematical relationship between the ocular elasticity, aqueous humor volume, and intraocular pressure has not been established. This review will briefly review recent literature on the pressure-related retinal pathophysiology in glaucoma and other pressure-induced retinal disorders, the elasticity of ocular tissues, and pressure-sensitive cation channels in retinal neurons. Emerging data support the global volume and the elasticity and thickness of the sclera and cornea as variables to affect the intraocular pressure level like the volume of the aqueous humor. Recent results also suggest some potential routes for TRPs to mediate transient depolarizing currents, and TRP vanilloid 4 concentration in retinal ganglion cells and extracellular glutamate concentration, inactivating voltage-gated Na\(^{+}\) channels, and causing excitotoxicity and dysfunction of retinal ganglion cells. Further studies on these routes likely identify novel targets and therapeutic strategies for the treatment of pressure-induced retinal disorders.

Key Words: glaucoma; ocular elasticity; patch-clamp; pressure-sensitive ion channel; retina; retinal bipolar cell; retinal ganglion cell; TRP

Introduction

Elevated intraocular pressure (IOP) is highly correlated with the retinopathy in glaucoma, and changes in the exterior pressure (EP) during mountain hiking, air traveling, and diving may also induce vision decline. The pathophysiological mechanism of these pressure-induced retinal disorders (PIRDs) has not been completely clear. Retinal neurons express pressure-sensitive ion channels intrinsically sensitive to pressure and membrane stretch, such as the transient receptor potential channels (TRPs) and the two-pore domain K channels. This article will briefly review the literature on the pathophysiology of glaucoma and other PIRDs, the elasticity of ocular tissues, and pressure-sensitive cation channels in retinal neurons. The strategy for searching the PubMed database: [neuron] OR [retina] OR [retinal] AND [pressure-sensitive] (OR [mechanosensitive]), [glaucoma] AND [retina] (OR [retinal] [aqueous humor]), [ocular pressure] AND [diving] (OR [hiking] OR [mountaineer] OR [flight] OR [astronaut]), [vision] OR [visual]) AND [pressure] (OR [diving] OR [hiking] OR [mountaineer] OR [flight] OR [astronaut]), etc. Google Scholar was used as an addition. Searches were performed mostly in and before 2019, and no date limit was applied. Reports more relevant to the topic and more comprehensive were preferentially selected.

Pressure-Induced Retinal Disorders

Glaucoma is a blinding disease characterized by the axon and soma loss of RGCs, involving multiple risk factors, such as age, race, genetic defects, glutamate excitotoxicity, etc. The elevation of the IOP, either the mean level or the fluctuation (Asrani et al., 2000; Caprioli and Coleman, 2008), has been accepted as the most significant risk factor (Quigley, 2011).

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Axons of RGCs form the optic nerve to carry visual signals to the visual cortex. Vision loss and RGC death in glaucoma are generally thought to follow IOP-induced optic nerve damage: IOP elevation → optic nerve injury → vision loss and RGC death. Studies from animal models have demonstrated that crushing the optic nerve can indeed retrogradely damage RGC somas. On the other hand, in human patients, the optical coherence tomography and immunobiological studies often show concurrent damage in the nerve fiber layer and RGC somas (Lei et al., 2008; Weinreb et al., 2014). In glaucoma animal models, recent anatomical and functional data support pathological changes in RGC dendrites (Berry et al., 2015; El-Din et al., 2015) and MGCs (van der Heijden et al., 2015). Since the number of bipolar cells (BCs) (Vrabec and Levin, 2007; Agostoni and Di, 2015; Ou et al., 2016), as well as the loss of highly sensitive BC inputs (Pang et al., 2015) in A2 amacrine cells and ON RGCs before RGC axon loss. These studies do not fully support that the early stage of IOP elevation can concurrently affect RGC axons, RGC dendrites, and BC synapses.

Glutamate excitotoxicity is a common mechanism for neurodegeneration, including glaucoma (Hare and Wheeler, 2009). However, whether BCs release more glutamate under elevated IOP to mediate RGC dendritic damage is unclear. Pressure-sensitive transient receptor potential channel vanilloid 4 (TRPV4) has been recently reported in mammalian retinal neurons. TRPV4 immunoreactivity was found in somas and axons of RGCs (Ryskamp et al., 2011; Jo et al., 2015; Gao et al., 2019) and the plexiform layers (Sappington et al., 2015; Taylor et al., 2016; Gao et al., 2019). We have recently observed TRPV4 expression in primates (Gao et al., 2019), where the pressure change/membrane expansion opens TRPV4 and induces transient cation currents with a reversal potential of ~−10 mV. The half-maximum effect appears at ~20 mmHg, in line with the clinical standard of elevated IOP. Others’ and our data (Ryskamp et al., 2011; Sappington et al., 2015; Taylor et al., 2016; Gao et al., 2019) have also revealed the functional TRPV4 in mammalian RGCs, and activating TRPV4 increases RGC spontaneous firing rate and the excitability. TRP-mediated membrane depolarization and Ca\(^{2+}\) influx are likely to mediate glutamate release in BCs and excitotoxicity in RGCs, which, as a novel mechanism for glaucoma RGC damage, deserves further investigations. Glutamate excitotoxicity is critically mediated by N-methyl-D-aspartate receptor and Ca\(^{2+}\), and N-methyl-D-aspartate receptor antagonists and Mg\(^{2+}\) have shown a neuroprotective role in RGCs. Mammalian Müller cells also express TRPV4, and opening TRPV4 depolarizes Müller cells (Jo et al., 2015; Netti et al., 2017), which is likely to reduce glutamate intake, increasing the extracellular glutamate concentration ([Glu]\(\text{net}\)) and triggering the excitotoxicity. Besides TRPV4, retinal neurons also express other types of pressure-sensitive channels, which will be further discussed in the last section.

Congenital glaucoma in children exhibits IOP elevation and the dramatic expansion of the eyeball and cornea (Ho and Walton, 2004; Papadopoulos et al., 2007). Stress and strain like IOP and tissue stretch are a pair of inseparable physical parameters capable of activating mechanical-sensitive ion channels. D2 mice develop congenital glaucoma and are widely used as a glaucoma model. D2 mice may exhibit either IOP elevation (Jakobs et al., 2005), IOP elevation plus eyeball expansion, or normal IOP with eyeball expansion (Pang and Wu, 2014), and RGC loss was observed under these conditions. It has been unclear whether the ocular expansion occurs in normal-tension glaucoma to mediate retinopathy like IOP dose in high-tension glaucoma. Normal-tension glaucoma consists of typical glaucomatous disc and field changes, an open angle, and IOP within the statistically normal range. It has been related to changes in the blood pressure and intracranial pressure, transmigrain pressure gradient (Killer and Pircher, 2018), migraine, shock, blood loss, optic disc hemorrhages, etc. (Anderson, 2011). Reducing IOP is also beneficial for some normal-tension glaucoma patients, but the mechanism is unclear.

Changes in the external pressure (EP) for the eye may also affect IOP and vision (Van de Veire et al., 2008). The elevation caused by acute drop in the atmospheric pressure (101 kPa at the sea level) has been reported to cause low visual acuity, blur vision, visual field defect, and vision loss (McFadden et al., 1981; Heddax and Butler, 2012) in mountain hikers at 84–75 kPa (Tingay et al., 2003; Horng et al., 2008; Ho et al., 2011), as well as flight passengers (Chang et al., 2004) and pilots (Vecchi et al., 2014) at 93–88 kPa. The capability of teenagers (Karakučuk et al., 2004) to differentiate colors reduces at 91 kPa. Under enhanced EP during diving, it is very common to see retinal damage, too. The standard diving depths for creation and technical divers are below 18 and 50 m (300 and 600 kPa), respectively. About 50% of professional divers show various degrees of retinal lesions (Zhou et al., 2014), and 45% show blue-yellow color vision defect (Macareza et al., 2005). Transient vision loss occurs in some individuals during or after diving (Heddax and Butler, 2012; Mowatt and Foster, 2013), which sometimes may completely and immediately recover upon surfacing (Heddax and Butler, 2012). While some structural retinal damage has been documented under these pathological conditions, brief RGC dysfunction or the direct disturbance of pressure on visual signals has not been ruled out. Pressure stress is the primary cause of PVRDs, but the roles of retinal pressure-sensitive ion channels in PVRDs have not been clear.

Chronic ophthalmic changes occur after spaceflight, including the reduction of near visual acuity, changes in the choroid and retina tissues, optic disk edema (Taibbi et al., 2013), a hypoxic shift of refraction, an increase of IOP, and an increase of intracranial pressure (Makarov et al., 2013). These disorders are usually attributed to the loss of the gravity or microgravity, posture changes, and the change in the transmigrain pressure (Nelson et al., 1985; Berdahl et al., 2012; Taibbi et al., 2013). Except for the gravity change, EP for the eye in space suits is reduced for 71% for the space shuttle era (to 30 kPa) and 43% for space station era (to 57 kPa) per the data in the space educators’ handbook from NASA. Whether the lowering of EP may contribute to the ophthalmic changes in astronauts has been unknown.

### The Elasticity of the Spherical Shell of the Eye

IOP in human eyeballs is normally 10–21 mmHg (1.3–2.8 kPa) higher than the atmospheric pressure. IOP is primarily determined by the volume of aqueous humor and expressed per the data in the space educators’ handbook from NASA.

\[ P(IOP) = P_e + (F_r - F_0)/C_{trab} \]

(Kaufman, 2011), where \( P_e \) is the episcleral venous pressure, \( F_0 \) is the outflow rate/formation rate, and \( C_{trab} \) is the facility of the outflow through the trabecular pathway. Aqueous humor formation involves active transportation/secretion, ultrafiltration, and diffusion, while a majority of aqueous humor is produced by active transportation and not pressure-dependent. The circulation of the aqueous humor acts to stabilize IOP, but IOP still fluctuates with the heartbeat, breath, and exercise. It shows 2–3 pulses/s in primates (Downs et al., 2011), and the amplitude is up to 10 mmHg and larger under higher IOP levels. IOP also fluctuates 2–6 mmHg with circadian rhythm (Liu et al., 1999; Sugimoto et al., 2006; Li and Liu, 2011). The normal flow rate of the aqueous humor is 2–2.5 μL/min, which falls by ~60% during the nighttime (Sit et al., 2008; Fan et al., 2011). \( F_0 \) is measured 1.64 μL/min in normal subjects of 20–30 years, 1.16 μL/min in normal subjects of 60 years, and 0.3 μL/min in normal subjects of 80 years (Toris et al., 1999; Kaufman, 2011). Water has a bulk modulus \( K \) of 2.2 × 10\(^6\) Pa. Assuming that the eyeball shell is not expandable, all eyeball contents are composed of water, and the eyeball inner volume \( V \) is 4.96 mL, every 1 μL of...
an extra amount of aqueous humor (ΔV) would elevate IOP for 500 mmHg (ΔP = K × ΔV/V). However, such hypothetic IOP fluctuation does not occur, and clinical IOP elevation is usually much less intensive. This is probably due to the elasticity of the eyeball shell.

IOP is a physical parameter of the eyeball. To better understand the harmful effect of the accumulation of aqueous humor in glaucoma, we still need to learn other physical properties of the eyeball. The elasticity or stiffness is defined by the ratio of the stress to the strain/deformation in the elasticity regime. E (Young’s), G (shear), and K (bulk) modulus can be calculated simply by:

\[ E = (F \times l)/(A \times Δl), G = (F \times l)/(A \times Δl), \text{ and } K = (F \times V)/(A \times ΔV). \]

Where F/A or P is the linear, shear, and volumetric stress for E, G, and K, respectively, and Δl/Δl, Δl, and V/ΔV are the linear, shear, and volumetric strain, respectively. In the human, E was measured 2.45 × 10^10 Pa in the cornea in vivo (Sjontoft and Edmund, 1987), 6.0 × 10^10 Pa in strips of choroidal complex, and 1.8–2.9 × 10^10 Pa in sclera strips (Friberg and Lace, 1988; Eilaghi et al., 2010). In freshly isolated pig eyeballs, it was 0.5–2.4 × 10^10 Pa for the cornea and 1.5–8.3 × 10^10 Pa for the sclera (Asejczyk-Widlicka and Pierscionek, 2008). In mouse eyeballs, scleral stiffness was measured 0.36–3.2 × 10^6 Pa and the initial length of tissue as 0.6–3 × 10^6 Pa and 1.8–2.9 × 10^6 Pa in sclera strips (Friberg and Lace, 1988). In Human eyeball was reported to be ~6.5 mL for the total volume, ~1 mm for the sclera thickness (h), and 310 μL (Va) for the aqueous volume, which gives an eyeball inner volume (V) of 4.96 mL and a radius (R) of 10.58 mm. Taking E of the ocular tissue as 0.6–3 × 10^10 Pa and the initial length l as 10.58 mm, every 10 mmHg increase of pressure (ΔP) would theoretically linearly stretch the tissue for ~155–777 μm (Δl = (σ × l)/E, σ = (ΔP × R)/2 × h, where σ is the circumferential stress). Interestingly, this theoretical value is well comparable with the calculated stretch on RGC axons induced by the optic disc cupping in chronic glaucoma (~70–646 μm, derived from (Shin et al., 1989; Sigal et al., 2004)).

Ephaptic communication occurs in mouse RGCs, the inner nuclear layer, amacrine cells, and the outer plexiform layer in the rat retina (Wang et al., 2010). TRPC6 agonists significantly reduce the repercussion-induced RGC death (Wang et al., 2010). TRPC6, TRPV1, and TRPV4 have a similar Pca/PNa ratio, but those located in BCs and amacrine cells presumably have opposite effects on RGCs. To better understand the PIRs in PIVDs, we need to better differentiate the roles of presynaptic and postsynaptic TRPs in RGC physiology, acute pressure responses, and the chronic pathologies in PIVDs.

### Pressure-Sensitive Ion Channels in Retinal Neurons

Pressure and membrane stretch are suitable stimuli for some ion channels expressed in the plasma membrane of cells, and these channels can be directly opened by force (Liu and Montell, 2015), known as mechano-gated or mechanical sensitive channels. TRPs are variably modulated by temperature, membrane tension, osmolality, phosphor esters, and G-protein-mediated regulation (Clapham, 2007; Liu and Montell, 2015). TRPs include seven subfamilies, namely TRPC (canonical), TRPV, TRPM (melastatin), TRPN (NOMP-C), TRPA (ANKT1), TRP2 (lovoctylin), and TRPML (mucolipin) (Montell, 2005; Nilius and Szallasi, 2014). The retina expresses multiple types of TRPs and TRPV4 (Tan et al., 2006; Krizaj, 2016) and TRPV1 (Sappington et al., 2015) have been suggested to contribute to glaucoma. TRPV4 opens by pressure (Suzuki et al., 2003), membrane stretch (Liedtke et al., 2000), warm temperature and specific pharmacological agonists like GSK1016790A (GSK) and 4 alpha-phorbol 12,13-didecanoate (4_PDD) (Nilius and Szallasi, 2014). TRPV4 is expressed in mammalian RGCs, BCs, Müller cells, and the plexiform layers. In our recent data, TRPV4 immunoreactivity in the primate retina exhibited a low-intensity component in Müller cells and amacrine cells and a high-intensity component in plexiform layers, and RGCs and BCs showed both the components. TRPV4 agonists increase the spontaneous firing rate of mouse RGCs and moderate apoptosis of cultured RGCs (Ryskamp et al., 2011). TRPV4 antagonists enhance RGCs survival rate in retinal explants (Taylor et al., 2016). Large RGC somas are more vulnerable than smaller ones in glaucoma patients and animal models (Glovinsky et al., 1991; Quigley, 1999; Shou et al., 2003; Filipopoulos et al., 2006), and the large somas in the primate retina possess heavier TRPV4 immunoreactivity in our results (Gao et al., 2019). These data support the idea that retinal TRPV4 could probably contribute to glaucoma RGC death. Glaucoma animal models showed a decrease in retinal TRPV4 expression (Sappington et al., 2015) and RGC firing rate (Della et al., 2013), consistent with the loss of RGC somas and BC synapses.

**Potential Routes for Retinal Transient Receptor Potential Channels to Mediate Retinal Ganglion Cell Pathophysiology in Glaucoma**

The role of retinal TRPs in glaucoma has not been certain.
Figure 1 | Diagram of potential routes for TRPs to mediate RGC pathophysiology in glaucoma.

Ocular physical parameters are depicted in A–C: E: Young’s modulus; EP: external pressure; IOP: intraocular pressure; P: pressure; V: eyeball volume; Va: volume of aqueous humor. In D, arrow: excitatory glutamate synapse; All: All amacrine cell; and butterfly shape: gap junction. In D and E, BC: rod bipolar cell (BC); BC: cone bipolar cell; MC: Müller cell; Type I and II nitroergic amacrine cell (NI and NII) and RGC: retinal ganglion cell. E displays the possible (arrow) and presumable (dashed arrow) effect of TRP activation upon increasing V and IOP, and three potential pathophysiological routes are illustrated involved by BC (1), RGC (2), and MC (3). TRP activation is known to cause influxes of Na$^+$ and Ca$^{2+}$, higher [Ca$^{2+}$], and the reduction of Na$^+$ electrochemical gradient ([Na$^+$]g), membrane depolarization, which are to be superimposed on light-evoked activities driven by the photoreceptor rod (R) and cone (C) and mediated by iGluRs in RGCs. Higher [Ca$^{2+}$], presumably increases glutamate (Glu) release in BCs, and in Müller cell (MC) TRP-mediated decrease of [Na$^+$]g would reduce Glu transportation by the excitatory amino acid transporter (EAAT) to increase [Glu]. The increased [Glu] can activate N-methyl-D-aspartate receptor (NMDAR) in RGCs, damaging RGC mitochondria via Ca$^{2+}$ and other excitotoxic mechanisms. The increase of [Ca$^{2+}$]g and [Na$^+$]g needs to consume more ATPs to restore their normal electrochemical gradients. Two potential pathophysiological cycles (I and II) are further proposed for RGCs. Cycle I anticipates that an extra amount of Na$^+$ influx would cause more ATPs to cause or enhance ATP shortage, and a dramatic reduction of [Ca$^{2+}$]g to further damage the mitochondria, causing or enhancing ATP shortage to further increase [Ca$^{2+}$]g and exacerbate the cellular damage.

Opening TRPs can increase [Ca$^{2+}$]g, and [Na$^+$]g, and reduce Na$^+$ electrochemical gradients [Na$^+$]g. Increased [Ca$^{2+}$]g has been known to mediate neuronal degeneration, while the energy stored in the normal [Na$^+$]g is critically required for the generation of action potentials and postsynaptic potentials mediated by GluRs, glutamate transportation by the excitatory amino acid transporters, and the extrusion of Ca$^{2+}$ by Na$^+$-Ca$^{2+}$ exchanger (Attwell and Laughlin, 2001; Howarth et al., 2012). Na-Ca exchanger imports 3 Na$^+$ to extrude 1 Ca$^{2+}$, transportation of each glutamate molecule is coupled with the co-transportation of 3 Na$^+$ (Bouverie et al., 1992; Arriza et al., 1994; Wadiche et al., 1995), and the opening of GluRs also induces Ca$^{2+}$ and Na$^+$ influxes. Cells rely on Na, K-ATP pump to maintain a normal [Na$^+$]g, which is powered by mitochondria and consumes 1 ATP to extrude 3 Na$^+$. While the membrane is depolarized above ~40 mV (Armstrong, 2006; Maier et al., 2002), the voltage-gated Na$^+$ channel is largely inactivated, and the activation and inactivation of voltage-gated Na$^+$ channel also can be modulated by membrane stretch (Morris and Juranka, 2007) and TRPV4 activation (Gao et al., 2019). Based on these classic concepts and current studies on TRPs, I propose three potential routes for retinal TRPs to mediate RGC pathophysiology in glaucoma, which are to be participated by BCs, RGCs, and Müller cells and primarily involved by the glutamate release from BCs and Ca$^{2+}$ and glutamate-mediated excitotoxicity, mitochondria damage, and the inactivation of voltage-gated Na$^+$ channels in RGCs (Figure 1).

Retinal neurons are not just the victim of elevated IOP, and they have shown some potential to influence IOP. First, vision is known to critically mediate the pupillary and accommodation reflex, whose effectors are the ciliary and iris muscles, respectively. The accommodation has been found to raise IOP in some patients (Yan et al., 2014; Aggarwala, 2020). Ciliary muscle contraction leads to distension of the TM with a subsequent reduction in outflow (an increase of IOP), while the contraction of iris muscles and TM leads to the opposite effect (Wiederhold et al., 2000). TM expresses mechanosensitive TRPV4, TREK1, and BK(Ca) channels (Dismuke and Ellis, 2009; Ryskamp et al., 2016; Yarishkin et al., 2018). Besides, Multiple types of neurotransmitter receptors have been observed in the ciliary and iris muscles, such as muscarinic cholinergic receptors, dopaminergic receptors, and adrenergic receptors. Thus, IOP and the circulation of aqueous humor can be affected by retinal light signaling, and the circulation and nervous systems. Whether the dysfunction of RGCs in the early glaucoma stage facilitates IOP elevation as anticipated requires further investigation in the future.

Second, nitric oxide (NO) donor has been shown to decrease IOP by increasing aqueous outflow facility in TM and Schlemm’s canal (Dismuke et al., 2008). NO may be released by retinal nitroergic amacrine cells (NOACs), which express the neuronal nitric oxide synthase. Two subtypes of NOACs (NI and NII) are nearly evenly distributed in the retina and receive excitatory glutamatergic synapses from BCs (Pang et al., 2010). Given the anatomical proximity, I anticipate that the presumable TRP-mediated glutamate release from BCs could enhance NO release from NOACs, serving as a compensative mechanism to suppress IOP elevation. NO is a free-radical gas, involving multiple retinal neuronal activities and glaucoma retinal pathology (Pang et al., 2010; Allency et al., 2017). The significance of retinal TRPs and NOACs in glaucoma needs further investigation.

Pressure-sensitive ion channels in retinal neurons can open upon pressure and membrane stretch, but their roles in retinal physiology and pathology have not been clear. To facilitate the channel therapy to be used in clinical treatment and promote vision health, we still need to better determine the normal role of these channels in retinal light signaling, the interaction between different types of the channels, and the effective channel modification capable of reducing IOP and the vulnerability of RGCs to IOP elevation. Future studies in this direction are likely to bring out novel mechanisms for PIVDs and novel cellular and molecular targets for clinical treatment of RIVDs.

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