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Degeneration of retina-brain components and connections in glaucoma: Disease causation and treatment options for eyesight preservation

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ABSTRACT

Eyesight is the most important of our sensory systems for optimal daily activities and overall survival. Patients who experience visual impairment due to elevated intraocular pressure (IOP) are often those afflicted with primary open-angle glaucoma (POAG) which slowly robs them of their vision unless treatment is administered soon after diagnosis. The hallmark features of POAG and other forms of glaucoma are damaged optic nerve, retinal ganglion cell (RGC) loss and atrophied RGC axons connecting to various brain regions associated with receipt of visual input from the eyes and eventual decoding and perception of images in the visual cortex. Even though increased IOP is the major risk factor for POAG, the disease is caused by many injurious chemicals and events that progress slowly within all components of the eye-brain visual axis. Lowering of IOP mitigates the damage to some extent with existing drugs, surgical and device implantation therapeutic interventions. However, since multifactorial degenerative processes occur during aging and with glaucomatous optic neuropathy, different forms of neuroprotective, nutraceutical and electroceutical regenerative and revitalizing agents and processes are being considered to combat these eye-brain disorders. These aspects form the basis of this short review article.

1. Introduction

The eyes are uniquely constructed organs of sensory perception using a combination of light, chemical and electrical forms of neuronal communication to permit perception of the environment around us. The optic nerve connecting the retina to the thalamic brain nuclei is one of the longest nerves within the central nervous system (CNS) (Fig. 1) and is subject to damage by many endogenous and exogenous factors. As with any complex organ, the eye contains many specialized cells and tissues with important functions which are disrupted during aging and which succumb to disease-related degenerative processes. One of the most prevalent eye diseases that is responsible for different levels of visual impairment and which can cause blindness is glaucoma (Weinreb et al., 2014; Sharif, 2017, 2018a, 2021), a group of optic neuropathies. Damage to the optic nerve causing retrograde retinal ganglion cell (RGC) and anterograde brain neuronal death represent the major features of such glaucomatous optic neuropathies (GONs). Since different forms of glaucoma exist (Weinreb et al., 2014; Sharif, 2017, 2018a, 2021), this review with focus on the most common forms, primary open-angle glaucoma (POAG; afflicting ≤80 million world-wide; Tham et al., 2014) and normotensive glaucoma (NTG; which predominates in Japan) to illustrate the factors, cells and processes involved or implicated in the disease initiation and progression (Weinreb et al., 2014; Sharif, 2021).

2. Primary open-angle glaucoma (POAG)

In order to better understand the ocular diseases to be discussed, the basic anatomical features and physiological elements of the eye need to be understood. . Simplistically speaking, the eye can be divided into the

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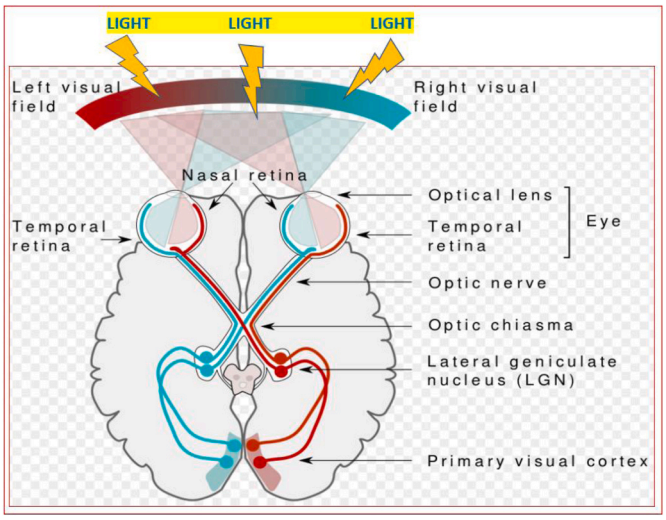

Fig. 1. Anatomical location and connections between the eyes and the brain structures involved in visual information capture, transmission and perception upon decoding.

anterior segment whose chamber is filled with aqueous humor (AQH) fluid that is formed by the ciliary body and that nourishes the cells of the lens, corneal endothelium and iris. The AQH then flows out through the trabecular meshwork (TM) and Schlemm's canal (SC) into the veinous circulation (Fig. 2). It is also the AQH that helps maintain the shape of the eyeball, and delivers nutrients, oxygen, antimicrobial agents and anti-oxidants to the tissues lining the anterior chamber of the eye. The posterior segment contains vitreous humor made up of proteins and water and is a gelatinous material that also helps preserve the eyeball shape and provides a cushioning support to the retina/choroid lining the inner wall of the posterior segment.

Advancing age (beyond 40-years), family history, poor retinal blood flow, low intracranial fluid pressure, diabetes and elevated intraocular

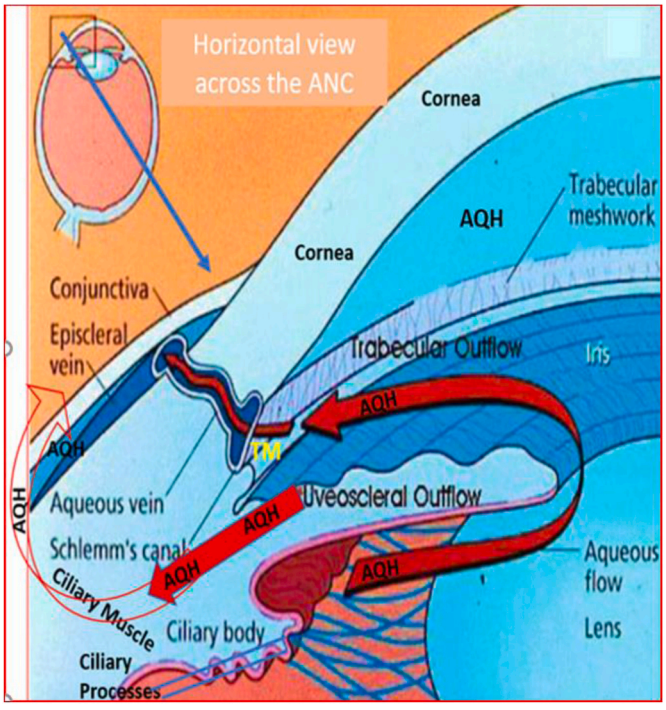

Fig. 2. Cartoon of the anterior segment of the human eye depicting key structures producing and draining the AQH is shown.

pressure (IOP; ocular hypertension) are risk factors associated with POAG. The ocular hypertension occurs when the TM/SC region in the anterior segment of the eye becomes congested with excessive cellular debris and extracellular matrix (ECM) which is normally phagocytosed and degraded by the TM cells. The aging process, excessive Ca^{2+}-accumulation within the TM cells, energy depletion of the latter and the stress caused by the accumulated cellular waste within and outside the TM cells rigidifies and eventually kills some of the TM cells (Abu-Amero et al., 2006; He et al., 2008, 2019; Rao et al., 2019). This reduces the ability of AQH to drain out from the anterior segment and as its volume increases, and the IOP continues to rise. Even though these processes occur very slowly and over decades, the elevated IOP stresses and strains all cells and tissues, in particular RGC axons at the optic nerve head (ONH; Hernandez et al., 1989; Burgoyne et al., 2005; Xu et al., 2014; Ju et al., 2015; Maddineni et al., 2020) and the delicate lamina cribosa tissue (LCT; Daguman and Delfin, 2018) of the inner most retina and the associated capillary network of the retinal arteries and veins. The mechanical distortion/distension/constriction of the latter ocular tissues and blood vessels leads to local inflammation (Soto and Howell, 2014; Ha et al., 2015; Williams et al., 2017b; Wei et al., 2019; Boia et al., 2020; Vernazza et al., 2020) and ischemia (Neufeld et al., 2002; Cho et al., 2011; Silverman et al., 2016) with a resultant hypoxic environment within the retina and the optic nerve (Fig. 3). Consequently, injurious chemicals (reactive oxygen species (McMonnies, 2018), nitric oxide and derivatives (Neufeld et al., 2002; Schneemann et al., 2003; Schnichels and Joachim, 2021), ATP (Resta et al., 2007; Hu et al., 2010), glutamate (Wamsley et al., 2005; Nguyen et al., 2011; Fu and Sretavan, 2012; Ju et al., 2008, 2015), endothelin (Stokely et al., 2002; Howell et al., 2011; Von Zee et al., 2012; Chaphalkar et al., 2020), proteases (Chintala, 2006) and activated microglia/astrocytes invade the retina and the optic nerves (Neufeld, 1999; Yuan and Neufeld, 2001; Ebneter et al., 2010; Rashid et al., 2019) and further damage results to RGC axons, and within the brain visual centers (Duce et al., 2006; Sasaoka et al., 2008; Gupta et al., 2007; Calkins and Horner, 2012; Kasi et al., 2019; Trivedi et al., 2019; Lam et al., 2009; Martucci et al., 2020) (Fig. 3).

With severe restriction of axonal transport of essential nutrients, growth factors (Pease et al., 2000; Sposato et al., 2008; Crish et al., 2013; Berry et al., 2015) and mitochondria (Pease et al., 2000; Stokely et al., 2002; Fahy et al., 2016) from the brain down the optic nerves, the RGC somas begin to slowly die. As more and more RGCs and their axons atrophy (Figs. 4a and b), the retinal connections to the brain thalamus (lateral geniculate nuclei [LGN], and superior colliculi [SPC]) (Yucel et al., 2000, 2001; Gupta et al., 2007; Sasaoka et al., 2008; Bhandari et al., 2019; Dai et al., 2012; Fujishiro et al., 2020) begin to also diminish leading to appreciable visual impairment of the afflicted patient (Weinreb et al., 2014; Sharif, 2021). Noticeable loss of peripheral vision, missing visual images and a decrease in contrast sensitivity results (Crabb, 2016). In the natural history of the initiation and progression of POAG, at this stage the patient's retina has lost up to 40% of the original 1.4 million RGCs. Because the disease now progresses a little faster, it now becomes critical for the patient to be diagnosed and a regimen of topical ocular IOP-lowering medication started in order to reduce the damaging effect of the elevated IOP. Many clinical trials have unequivocally demonstrated the beneficial effects on vision preservation by permitting drainage of AQH and subsequent reduction in IOP (e.g. CNTGSG- Collaborative Normal-Tension Glaucoma Study Group, 1998a, b; Kass et al., 2002; Gazzard et al., 2003; Musch et al., 2011; Tu et al., 2019), which ultimately reduces the damage to the visual centers of the brain (Yucel et al., 2000, 2001; Gupta et al., 2007; Sasaoka et al., 2008; Lam et al., 2009; Dai et al., 2012; Sponsel et al., 2014; Yu et al., 2015; Bhandari et al., 2019; Fujishiro et al., 2020) (Fig. 5).

However, since some of the afore-mentioned deleterious elements and factors are IOP-independent, the damage to the eye-brain axis structures and some loss of their functionality continues unabated. It is fortuitous that neural plasticity allows the patient's visual system to compensate for the loss of so many RGCs and thus the patient's eyesight

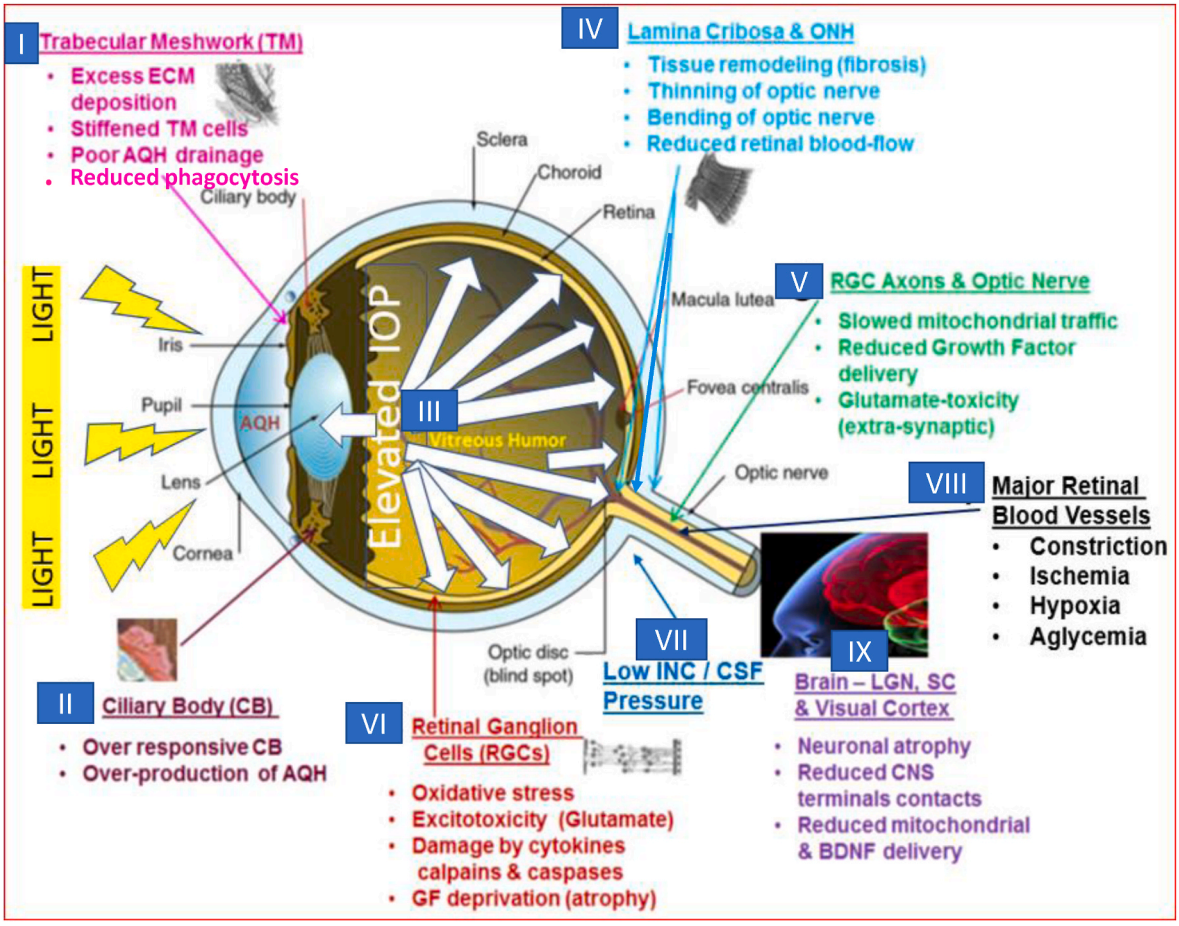

Fig. 3. Schematic illustration of the many sites of damage that can occur within the eye-brain axis due to chronically elevated IOP in POAG.

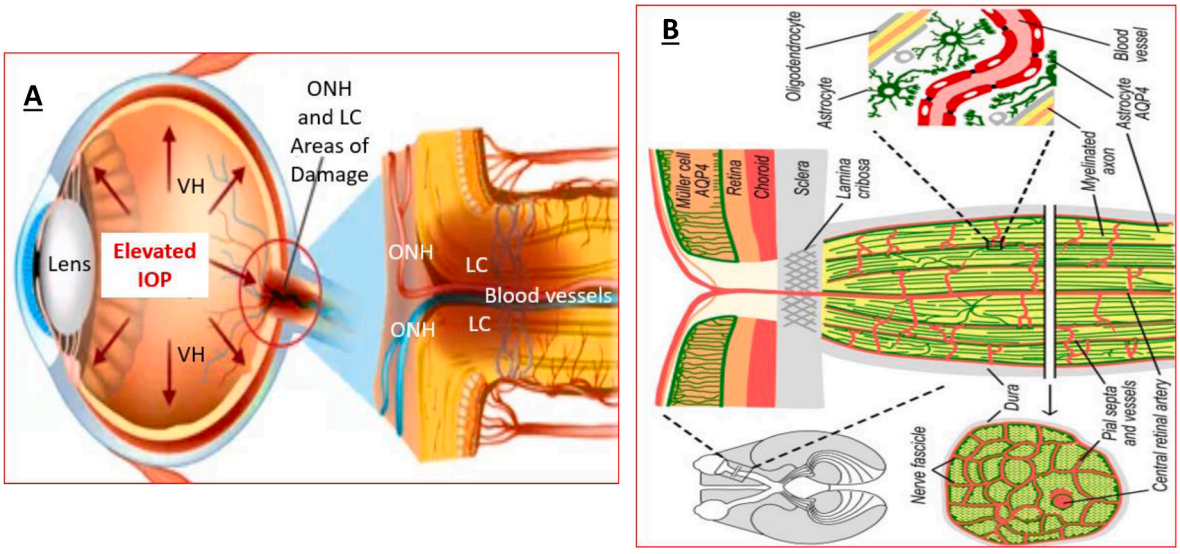

Fig. 4. Cartoon showing how raised IOP bulges the eye and causes mechanical pressure to radiate to all part of the eye but in particular how and where it causes damages at the ONH/LC regions (A). The molecular and cellular components affected by the elevated IOP at the level of the ONH/LC and optic nerve are depicted in more detail in panel B.

is stabilized and further deterioration temporarily slowed/halted (Bham et al., 2020). If the visual impairment continues, the clinician may change or add to the existing IOP-lowering medication, or recommend surgical intervention to remove excess AQH and to drastically lower the IOP. These aspects will be detailed ahead.

3. Normotension glaucoma and non-arteritic anterior ischemic optic neuropathy

Patients experiencing glaucomatous damage and vision loss despite having IOPs in the normal range (14–21 mmHg) are deemed to have

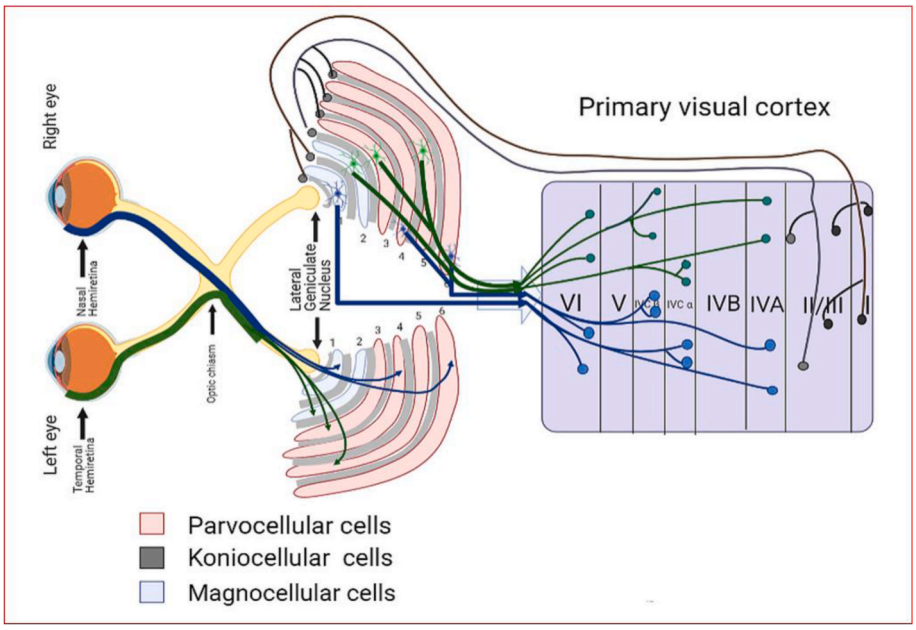

Fig. 5. The brain structures impacted by chronic ocular hypertension (OHT) or POAG at the lateral geniculate and visual cortical levels are shown.

"normotensive glaucoma" (NTG) or "normal-tension" or "low-tension glaucoma" (Hollander et al., 1995; Bhandari et al., 1997; CNTGSG-Collaborative Normal-Tension Glaucoma Study Group, 1998a,b; Park et al., 2015; Mallick et al., 2016; Zhang et al., 2019). It is unclear how and why the NTG patients' eyesight is adversely affected although a few clues have emerged. Some of the risk factors and features of NTG include poor retinal blood flow, sleep apnea, female gender, East Asian ancestry, low central corneal thickness, and poor nervous axonal flow (Kwon et al., 2017; Zarei et al., 2017; Hirooka et al., 2021). This condition may be worsened by heightened sensitivity of some RGCs and their axons to the prevailing hypoxia, neurotrophin and nutrient deprivation and neurotoxicity with a lowered level of recovery of injured or damaged RGCs and brain tissues. Whilst NTG patients benefit from drug/surgical-induced ocular hypotension (Bhandari et al., 1997; CNTGSG- Collaborative Normal-Tension Glaucoma Study Group, 1998a, b; Sehi et al., 2010), it is clear that other forms of therapeutic

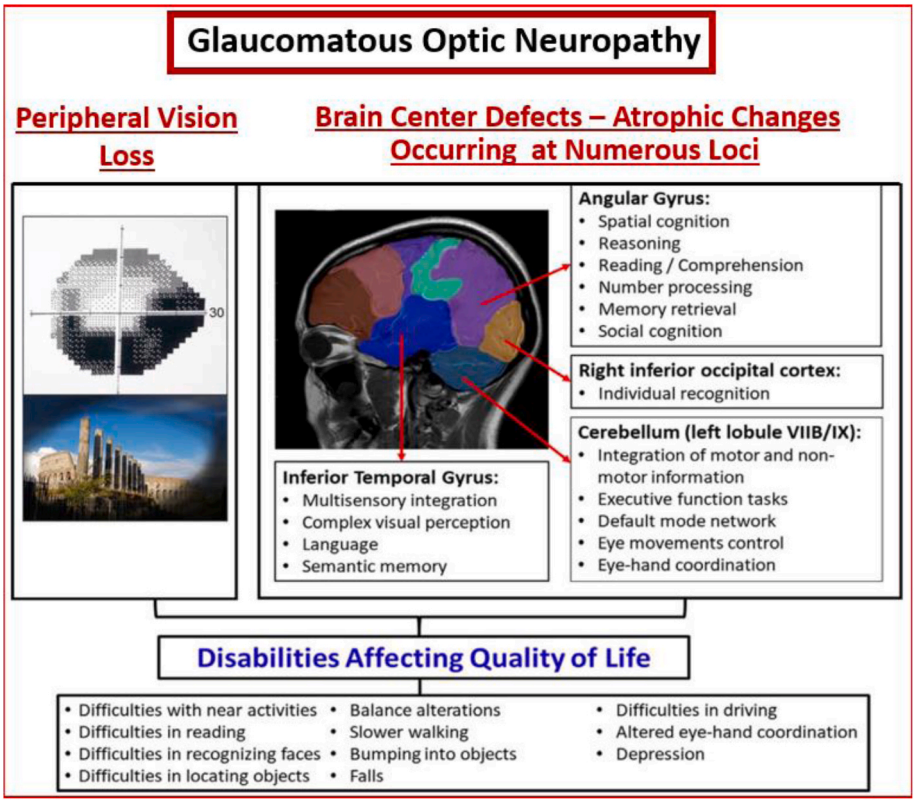

Fig. 6. The deleterious effects glaucomatous optic neuropathy (GON) on retinal and brain structures and their dysfunctions resulting in various disabilities are depicted.

intervention are needed that can directly slow down RGC/RGC axon and thalamic and cortical neuronal cell damage and help preserve eyesight. The many disabilities caused by chronically elevated IOP, POAG/NTG involve ocular and CNS centers responsible for visual outcomes (Fig. 6).

Another example of IOP-independent optic nerve-damaging disease is nonarteritic anterior ischemic optic neuropathy (NAION; Bernstein et al., 2011; Johnson et al., 2021) which suddenly develops in people over 50-years of age and accounts for >10 k cases/year in the USA. The ischemic insult triggers RGC axonal damage, RGC loss and subsequent demyelination of the optic nerve with little hope of recovering lost axons and vision. Such recovery is often prevented by the release of chemicals and proteins such as Nogo-A which is a myelin-associated neurite outgrowth inhibitor which inhibits axonal regeneration via a specific receptor (Chen et al., 2000). Unfortunately there is no current treatment for NAION.

4. Existing and future treatment options for POAG/NTG and NAION

4.1. Ocular hypotensive drugs

As described above, a diverse set of clinical trials have demonstrated a strong correlation between chronically elevated IOP, loss of RGCs, ONH /LC damage (and loss of supporting tissue in these regions), brain structural and functional defects, and visual field deterioration in glaucoma patients (CNTGSG- Collaborative Normal-Tension Glaucoma Study Group, 1998a,b; Kass et al., 2002; Heijl et al., 2002; Gazzard et al., 2003; Musch et al., 2011; Tu et al., 2019) and in non-human primates (Sasaoka et al., 2008; Lambert et al., 2019; Tu et al., 2019). Furthermore, many population-based studies have demonstrated that lowering of IOP retards the progression of GON and slows down loss of visual acuity, contrast sensitivity and overall visual defects (CNTGSG-Collaborative Normal-Tension Glaucoma Study Group, 1998a; Kass et al., 2002; Heijl et al., 2002; Musch et al., 2011). This knowledge prompted and succeeded in discovery, development and eventual worldwide approvals of drugs (e.g. see Weinreb et al., 2014; Toris et al., 2008; Sharif, 2021, Table 1), laser-based (Geffen et al., 2017; Garg and Gazzard, 2018) and other surgical (Sehi et al., 2010; Kwon et al., 2017) and tube/microshunt-based therapies (Pillunat et al., 2017; Sadruddin et al., 2019) to lower and control IOP.

The last two decades' drug discovery efforts have yielded potent and efficacious IOP-lowering drugs such as: 1). AQH inflow inhibitors that reduce the production of AQH (e.g. beta-blockers [e.g. timolol]; carbonic anhydrase inhibitors [e.g. dorzolamide]; alpha-adrenergic agonists [e.g. brimonidine]) (Civan and Macknight, 2004); 2). AQH outflow stimulator drugs (e.g. muscarinic agonists [pilocarpine]; rho kinase inhibitors (e.g. ripasudil; Futakuchi et al., 2020) and netarsudil (Lin et al., 2018; Asrani et al., 2020)]; 3). first-line medications that mainly promote uveoslceral outflow of AQH from the anterior segment of the eye (via newly generated spaces between ciliary muscle and the sclera), with some conventional outflow inducing actions (Toris et al., 2008) (e.g. FP-prostaglandin receptor agonists [e.g. latanoprost and travoprost]; Hellberg et al., 2002; Klimko and Sharif, 2019) (Table 1). Due to genetic predisposition or other factors, some glaucoma patients are resistant to FP-agonists and/or have decreased responsiveness to one or more topical ocularly delivered drugs to lower and control their IOPs. For such recalcitrant patients, drugs conjugates such as latanoprostene (nitric oxide donor coupled to latanoprost; Addis and Miller-Ellis, 2018) and various combination drug products are now available (Hollo et al., 2014; Asrani et al., 2020). In terms of the future drug development prospects, many emerging drug candidates with diverse targets and mechanisms of action have shown effectiveness in animal models of POAG and are progressing towards clinical proof-of-concept trials. These encompass, for instance, serotonergic agonists of 5HT2 receptors (May et al., 2015), non-peptide agonist bradykinin receptor stimulators (Sharif et al., 2014), stimulators of K^+-ion-channels (Roy Chowdhury et al., 2017), transient receptor voltage-gated channel inhibitors (Sappington et al., 2015; Ryskamp et al., 2016; Uchida et al., 2021; Li et al., 2021), natriuretic peptide receptor agonists (Savinainen et al., 2019), activators of guanylate cyclase (Dismuke et al., 2009, 2010), beta-receptor silencing RNA-based molecules (Gonzalez et al., 2014), etc., etc. (Table 2).

Fortuitously, some of the health authority-approved ocular hypotensive drugs also possess direct neuroprotective activity as shown in cell-based and animal models of neurodegeneration, but it is uncertain whether these beneficial properties will be realized in human subjects in a reproducible manner. Unfortunately, the translatability of neuroprotection by some clinically tested agents has not been completely fruitful (Levin et al., 2017; Weinreb et al., 2018) but requires continued effort since better designed trials are becoming increasingly available with potential new diagnostic and prognostic biomarkers/potential surrogate end-points using novel technologies (e.g. optical coherence tomography-angiography (OCT-A) (Rabiolo et al., 2021), OCT-coupled with adaptive optics (Bower et al., 2021); metabolic measurements *in vivo* (Geyman et al., 2018; Garg et al., 2021) and visualizing and quantifying dying retinal cells using fluorescence technologies (Cordeiro et al., 2021) and other types of dyes (Tsuda et al., 2016).

4.2. Laser and surgery-based treatments for POAG/NTG

Glaucoma patients whose IOPs remain uncontrolled despite maximally tolerated drug treatment have to undergo procedures with lasers (Geffen et al., 2017; Garg and Gazzard, 2018) or physical knife-based surgery (Sehi et al., 2010; Kwon et al., 2017) to drain the excess AQH in their eyes. There is a long history of use of these last-resort treatment options with significant beneficial improvements in patient visual fields (Geffen et al., 2017; Sehi et al., 2010; Kwon et al., 2017; Garg and Gazzard, 2018), presumably due to slowing down of their RGC death (Harwerth and Quigley, 2006) and decreased vulnerability of RGC axonal and brain neuronal atrophy (Yucel et al., 2000; Gupta et al., 2007, Figs. 5 and 6) that is associated with chronic ocular hypertensive/POAG and other forms of GON (Sharif, 2017, 2018a,b).

4.3. AQH drainage microshunt-based treatment of POAG/NTG

Many types of AQH drainage tubes (Le et al., 2021; Collar et al., 2021) and microshunts (Pillunat et al., 2017; Sadruddin et al., 2019) have been successfully deployed to lower and control IOPs in ocular hypertensive and glaucoma patients. Some of the recently introduced microshunts are capable of reducing the IOP down to 10–13 mmHg over several years after implantation of the minimally invasive glaucoma surgery (MIGS) devices (Pillunat et al., 2017; Sadruddin et al., 2019) with improved visual acuity outcomes (Sadruddin et al., 2019). These novel methods and devices also reduce the dependence on topical ocularly delivered IOP-lowering drugs without impacting the ocular health of the patients and will ultimately improve patient compliance. The latter issue is important to consider since the glaucoma patients tend to be elderly and experience infirmity, forgetfulness and general aversiveness to administering drugs that have bothersome ocular side-effects such as burning, stinging, significant eye redness, allergic reactions and iridial color changes, "sunken eye appearance", unevenly thickened and lengthened eyelashes, etc (e.g. Alm et al., 2008; Yeh et al., 2021; Sakata et al., 2021).

4.4. Nutraceutical aspects of glaucoma/GON treatments

As mentioned above, many detrimental IOP-independent factors and processes plague the patients with POAG and NTG. Likewise, with the knowledge that many food-derived compounds possess health-promoting properties, patients and their care-givers are increasingly modifying their diets and adding exercise to their daily routines. The concept of nutraceutical therapeutics for eye diseases started with the age-related eye diseases study (AREDS) where various vitamins and

Table 1
List of important ocular hypotensive medications used to treat ocular hypertension (OHT)/POAG/NTG.

Medication & Year of Clinical Introduction/FDA or Other Health Agency Approvals	Generic Name & Drug Type. (IOP reduction achieved in OHT/POAG patients)	Available Dosage (%, w/v)	Recommended Topical Ocular Dosing Frequency	Mechanism of Action to Lower IOP	Some Side-Effects/Adverse reactions
Stimulators of Conventional Outflow (TM/SC Route)					
Isopto carpine (USA Approval 1974); Pilopine	Pilocarpine (Agonist at muscarinic receptors; mostly M1)	Available as 1%, 2%, 4%; and as 4% Gel	Recommended dosage is 1 topical ocular drop ranging from 2-4-times/day and 1 application of gel across the eye	Stimulation of AQH drainage via TM/SC route	Miosis, irritation of ocular surface, brow-ache, accommodative problems, potential for heart-rate slowing, blurring of vision.
Isopto Carbachol	Carbachol (Agonist at muscarinic receptors; mostly M1)	Available as 1.5% and 3% solutions	Recommended dosage is 1–2 topical ocular drops up to 3-times on a daily basis	Stimulation of AQH drainage via TM/SC route	Miosis, irritation of ocular surface, brow-ache, accommodative problems, potential for heart-rate slowing, blurring of vision.
Glanatec (Approved in Japan 2014)	Ripasudil (Inhibitor of Rho kinase [ROCK]) (3.5–4.5 mmHg IOP lowering achieved)	Available as 0.4% solution	Recommended dosage is 1–2 topical ocular drops/day	Stimulation of AQH drainage via TM/SC route	Conjunctival irritation and allergic reaction, punctate keratitis and blepharitis
Rhopressa (Approved in USA 2017)	Netarsudil (Inhibitor of Rho kinase [ROCK]) (5 mmHg IOP reduction)	Available as 0.02% solution	Recommended dosage is 1 topical ocular drop/day	Stimulation of AQH drainage via TM/SC route; also lowers episcleral veinous pressure	Ocular redness, ocular pain, hemorrhage of conjunctival blood vessels, verticillata of cornea.
AQH Production Inhibitors					
Timoptic (USA approval in 1978) Timoptic-XE Gel	Timolol (Antagonist of beta-adrenoceptors in CB)	Available as 0.25%, 0.5% solutions or as a gel-forming formulation	Recommended dosage is 1–2 topical ocular drops/day	Inhibition of AQH production from CB.	Stinging, burning, itching, tearing, hyperemia, corneal keratitis, conjunctivitis, blurring of vision, refractive changes, blepharitis, dryness of ocular surface, lowered corneal sensitivity.
Betoptic (USA approval in 1985)	Betaxolol (Antagonist of beta-1- adrenoceptors)	Available as 0.25% suspension and a 0.5% solution	Recommended dosage is 1 topical ocular drop administered 2-times/day for 0.25% suspension, and 1–2 drops twice/day for the 0.5% solution	Inhibition of AQH production from CB.	Blurred vision, foreign body sensation, ocular surface dryness, ocular pain, decreased corneal sensitivity, ocular itch, decreased visual acuity, crusty lashes and photophobia, bradycardia, bronchospasm, pulmonaty distress, asthma and respiratory issues, insomnia, lethargy, depression, headache, dizziness.
Alphagan (USA approval in 1996)	Brimonidine (IOP reduced by 2–6 mmHg)	Available as 0.15% and 0.2% solutions	Recommended dosage is 1 topical ocular drop 3-times/day	Inhibition of AQH production from CB, and enhancement of UVSC outflow of AQH	Ocular allergy, conjunctival redness, ocular itching, stinging and burning, foreign body sensation in the eye, blurred vision, lethargy and drowsiness, eye pain.
Iopidine (USA approval in 1987)	Apraclonidine	Available as a 0.5% solution	Recommended dosage is 1–2 topical ocular drops 3-times/day	Inhibition of AQH production from CB	Hyperemia (redness), itching, tearing of the eye, Blurred vision or change in vision, chest pain, clumsiness or unsteadiness, depression, dizziness, eye discharge, irritation, or pain, irregular heartbeat. Ocular itch, tearing, eye discharge, ocular irritation, blurred vision, hyperemeia, clumsiness, depression, dizziness, irregular heartbeat, chest pain
Trusopt (USA approval in 1994)	Dorzolamide (Inhibitor of carbonic anhydrase)	Available as a 2% solution	Recommended dosage is 1 topical ocular drop 3-times/day	Inhibition of AQH production from CB	Eye irritation, burning, stinging, blurred vision, tearing, photophobia, superficial punctate keratitis, ocular surface dryness, transient bitter taste.
Azopt (USA approval in 1998)	Brinzolamide (Inhibitor of carbonic anhydrase)	Available as a 1% suspension formulation	Recommended dosage is 1topical ocular drop 3-times/day	Inhibition of AQH production from CB	Temporary ocular discomfort, temporary blurred vision, dry eye, hyperemia, ocular itching, foreign body sensation in the eye, headache, eye discharge, bitter, sour and unusual taste.
Enhancers of UVSC Outflow of AQH					
Xalatan (USA approval in 1996)	Latanoprost (Free acid is a selective agonist of the FP-prostaglandin receptors).	Available as a 0.005% solution	Recommended dosage is 1 topical ocular eyedrop at bedtime	Stimulates AQH egress via UVSC and TM/SC routes of drainage	Blurred vision, burning, stinging, itching, hyperemia, Iridial darkening, periocular skin coloration, foreign body sensation in the eye, uneven eyelash

(*continued on next page*)

Table 1 (*continued*)

Medication & Year of Clinical Introduction/FDA or Other Health Agency Approvals	Generic Name & Drug Type. (IOP reduction achieved in OHT/POAG patients)	Available Dosage (%, w/v)	Recommended Topical Ocular Dosing Frequency	Mechanism of Action to Lower IOP	Some Side-Effects/Adverse reactions
					thickening and lengthening, periorbital fat loss resulting in "sunken eyes look", eyelid discomfort due to crusting, and photophobia.
Travatan (USA approval in 2001)	Travoprost (Free acid is a highly selective agonist of the FP-prostaglandin receptors).	Available as a 0.004% solution	Recommended dosage is 1 topical ocular eyedrop at bedtime	Stimulates AQH egress via UVSC and TM/SC routes of drainage	Iris color darkening, periocular skin darkening, foreign body sensation, uneven eyelash thickening and lengthening, periorbital fat loss resulting in "sunken eyes look", eyelid discomfort due to crusting, and photophobia.
Lumigan (USA approval in 2001)	Bimatoprost (Free acid is a relatively selective agonist of the FP-prostaglandin receptors).	Available as a 0.03% solution	Recommended dosage is 1 topical ocular eyedrop at bedtime	Stimulates AQH egress via UVSC and TM/SC routes of drainage	Conjunctival redness, uneven thickening and elongation of eyelashes, iris darkening, periocular skin darkening, foreign body sensation, periorbital fat loss resulting in "sunken eyes look", eyelid discomfort due to crusting, and photophobia, and Hirsutism (a condition of hair growth on parts of the body normally without hair).
Taflotan (Japanese approval in 2008 J) Zioptan (USA approval in 2012)	Tafluprost (Free acid is a Relatively selective agonist of the FP-prostaglandin receptors).	Available as a 0.0015% solution	Recommended dosage is 1topical ocular eyedrop at bedtime	Stimulates AQH egress via UVSC and TM/SC routes of drainage	Hyperemia, foreign body sensation, ocular irritation, burning, dryness of ocular surface, tearing, iris darkening, periorbital skin darkening, uneven thickening and elongation of eyelashes, and photophobia.
Rescula (USA approval in 2000)	Unoprostone (free acid is a weak partial agonist at the FP-receptor)	Available as a 0.15% solution	Recommended dosage is 1 topical ocular eyedrop twice/day	Weakly stimulates AQH egress via UVSC outflow pathway, and perhaps via the TM/SC route of drainage	Iris and periorbital skin darkening, uneven thickening and elongation of eyelashes, eye burning, stinging, itching, corneal lesion, discharge, eye hemorrhage, ocular pain, irritation, blepharitis, keratitis with accompanying photophobia.
Eybelis (Japanese approval in 2018)	Omidenepag Isopropyl (Free acid is a non-prostaglandin EP2-receptor selective agonist)	Available as a 0.002% solution	Recommended dosage is 1 topical ocular eyedrop/day	Stimulates AQH outflow via both UVSC and TM/SC pathways.	Major ocular side-effects are transient redness of the conjunctiva and corneal thickening.
Fixed-Dose Combination Products Used to Treat OHT/POAG/NTG					
Cosopt (USA approval in 1998)	Dorzolamide & Timolol	Available as fixed dose (2% + 0.5%) formulation	Recommended dosage is 1 eyedrop 2-times/day	Inhibition of AQH generation at CB level	Side-effects included those induced by each of the drugs administered alone (see above)
Combigan (USA approval in 2007)	Brimonidine &Timolol	Available as fixed dose (0.2% + 0.5%) formulation	Recommended dosage is 1 eyedrop every 12 h	Inhibition of AQH generation at CB level	Side-effects included those induced by each of the drugs administered alone (see above)
Simbrinza (USA approval in 2013)	Brinzolamide & Brimonidine	Available as fixed dose (1% + 0.2%) formulation	Recommended dosage is 1 eyedrop 3-times/day	Inhibition of AQH generation at CB level	Side-effects included those induced by each of the drugs administered alone (see above)
Roclatan (USA approval in 2019)	Netarsudil & Latanoprost	Available as fixed dose (0.02% + 0.005%) formulation	Recommended dosage is 1 eyedrop/ day	Stimulation of AQH egress from ANC of eye via UVSC and TM/SC routes	Side-effects included those induced by each of the drugs administered alone (see above)
Xalacom	Latanoprost & Timolol	Available as fixed dose (0.005% + 0.5%) formulation	Recommended dosage is 1 eyedrop/ day	Stimulation of AQH egress from ANC of eye via UVSC and TM/SC routes, and by inhibiting AQH formation	Side-effects included those induced by each of the drugs administered alone (see above)
Duotrav	Travoprost & Timolol	Available as fixed dose (0.004% + 0.5%) formulation	Recommended dosage is 1 eyedrop/ day	Stimulation of AQH egress from ANC of eye via UVSC and TM/SC routes, and by inhibiting AQH formation	Side-effects included those induced by each of the drugs administered alone (see above)
Ganfort	Bimatoprost & Timolol	Available as fixed dose (0.03% +	Recommended dosage is 1 eyedrop/ day	Stimulation of AQH egress from ANC of eye	

(*continued on next page*)

Table 1 (*continued*)

Medication & Year of Clinical Introduction/FDA or Other Health Agency Approvals	Generic Name & Drug Type. (IOP reduction achieved in OHT/POAG patients)	Available Dosage (%, w/v)	Recommended Topical Ocular Dosing Frequency	Mechanism of Action to Lower IOP	Some Side-Effects/Adverse reactions
		0.5%) formulation		via UVSC and TM/SC routes, and by inhibiting AQH formation	Side-effects included those induced by each of the drugs administered alone (see above)
Taflotan + Timolol	Taflotan & Timolol (IOP-lowering observed were >13 mmHg; 40% reduction)	Available as fixed dose (0.0015% + 0.5%) formulation	Recommended dosage is 1 eyedrop/day	Stimulation of AQH egress from ANC of eye via UVSC and TM/SC routes, and by inhibiting AQH formation	Side-effects included those induced by each of the drugs administered alone (see above)
Additional Products Available for IOP-Lowering					
Vyzulta (Usa approval in 2017)	Latanoprostene Bunod (This is a conjugate drug composed of latanoprost and a NO-donor molecule)	Available as fixed dose (0.024% solution) formulation	Recommended dosage is 1 eyedrop at bedtime	Stimulation of AQH egress from the ANC via UVSC and TM/SC routes	Ocular irritation, eye redness, temporarily blurred vision, darkening of the iris, periocular skin darkening, uneven thickness and lengthening of eyelashes.
Durysta Implant (USA approval in 2020)	Bimatoprost-containing bioerodable polymer that is injected into the ANC of the eye	Not applicable here	Intracameral injection of the implant that contains the medication—sustained release occurs over 6-month period.	Stimulation of AQH egress from the ANC via UVSC and TM/SC routes	Some eye redness, eye pain, foreign body sensation in the eye, eye irritation, transiently increased IOP, some loss of corneal endothelial cells, blurred vision, headache, iritis, and some conjunctival hemorrhage.

other agents were shown to have a beneficial effect in age-related macular degeneration (AMD) patients (Camelo et al., 2020; Keenan et al., 2020). Since build-up of ECM and intracellular proteins and cellular debris in ocular hypertensive/POAG patients' anterior segment of the eye causes oxidative stress to the surrounding tissues, and ischemia injury at the back of the eye restricts blood flow due to bending and increased tortuosity of the retinal blood vessels in the same patients (and in NTG patients), exposure to or intake of oral antioxidants seemed a likely solution (Ammar et al., 2012; Buendia et al., 2015; Michalska et al., 2020). Likewise, other food- and natural product-derived substances (Adornetto et al., 2019, 2020) and vitamins (Williams et al., 2017b; Cammalleri et al., 2020; Hui et al., 2020) and other nutraceuticals (Morrone et al., 2018; Saccà et al., 2019; Chaudhry et al., 2021) were also deemed useful for patients with visual impairment due to ocular hypertension and glaucoma. In short, studies in various animal models of POAG/GON have demonstrated beneficial neuroprotective effects of polyunsaturated fatty acids (Saccà et al., 2019) and derivatives, curcumin, alpha lipoic acid (Inman et al., 2013), flavonoids, quercetin, green tea-derived epigallocatechin-3-gallate (Zhang et al., 2021), coenzyme Q, Ginkgo bilboa extracts and bilberry anthocyanins (Shim et al., 2012) Goji and other berries, resveratrol (Lindsey et al., 2015), and nicotinamide/vitamin B3 (Morrone et al., 2018; Saccà et al., 2019; Chaudhry et al., 2021). Indeed, vitamin B3 and pyruvate have proven effective in a recent clinical trials in ocular hypertensive/POAG patients where they improved the visual fields (Hui et al., 2020; De Moraes et al., 2022). This is a very promising outcome and requires confirmation in additional patient-based investigations, including those with NTG patients.

4.5. Electroceutical regenerative options for POAG/GON

Since ancient times, acupuncture and electrical brain stimulation have yielded benefits to patients suffering from pain and pathological depression or anxiety (Ma, 1992; Basser, 1999; Goldberg, 2012). The exact mechanisms of action of such treatments have remained elusive although new insights have been gained in recent years. As an extension of the latter concept, several studies demonstrated a therapeutic effect of transcorneal electrical stimulation in rodents and rabbits in enhancing survival of RGCs after optic nerve damage was induced (Morimoto et al., 2002, 2005; Miyake et al., 2007) with such protective effects also being exerted on photoreceptor cells (Morimoto et al., 2007, 2012) and preservation of inner retinal neurons (Schmid et al., 2009). Moreover, such electrostimulation resulted in preservation of visual function and much of the structural elements in follow-up studies where RGC axonal regeneration was observed (Pardue et al., 2014; Yang et al., 2016; Hanif et al., 2016; Lim et al., 2016). Many *in vitro* experiments using isolated RGCs, Muller glia and other cells (O'Hearn et al., 2006; Sato et al., 2008a,b; Huang et al., 2010; Ou et al., 2016; Enayati et al., 2020) and *in vivo* studies (Morimoto et al., 2005; Pardue et al., 2014) demonstrated up-regulation of neuroprotective transcriptional factors and release of endogenous protective neurotrophins (e.g. brain-derived growth factor; insulin growth factor), and a reduction of inflammatory agents and microglial activation (Zhou et al., 2016; Yin et al., 2016; Fu et al., 2018; Pardue et al., 2014) following electric stimulation. Furthermore, the axonal regeneration and RGC protection promoted by electrostimulation induced Muller cell proliferation (Enayati et al., 2020) and through stem cell neural differentiation (Cheng et al., 2021). Early clinical studies using alternating current stimulation in partially blind patients have shown a 24% improvement in visual fields that was durable out to 2-months (Gall et al., 2016). This appears to be due to neuroplasticity since low vision patients showed activation of the visual cortex, enhancement of global reorganization of brain networks and increased local blood-flow (Sabel et al., 2020). These encouraging results strongly support the utility of refined and graded electroceutical techniques and technologies to help preserve eyesight and potentially improve it. The concept of the bionic eye with retina-electrode interfacial characteristics, retinal prostheses and vision restoration (Yue et al., 2016) is certainly an inspiring and achievable goal. Further progress in this arena is eagerly awaited.

4.6. Prospects of gene therapy for POAG/NTG

Disease mitigation via genetic manipulation is a well-accepted concept and a treatment paradigm for glaucoma now, after a slow

Table 2
Some newly discovered ocular hypotensive agents based on various rodent, rabbit and monkey models of ocular hypertension.

Type of compounds	Test compounds	Purported and confirmed modes of action
TM/SC outflow stimulators		
Chloride transport inhibitors/ cytoskeletal change inducers	Ethacrynic acid; Ticrynafen; Indacrinone	AQH egress is induced by blocking the chloride transport and/or by TM cell shape changes
Inhibitors of various kinases	Src kinase inhibitors; Chelerythrine; Staurosporin; Myosin-II ATPase inhibitor: Blebbistatin. LIM-K inhibitors (e.g. LX7101)	All compounds block or reduce intracellular kinase enzymic activity to induce relaxation of the TM cells to promote AQH egress to lower IOP. These compounds may lack specificity and may cause more side-effects than selective rho kinase inhibitors.
Inhibitors of Rho kinase (ROCK)	AMA0076; ITRI-E-212 (older ROCK inhibitors include Fasudil and Y-27632)	These compounds are new generation ROCK inhibitors that relax the TM structure to help AQH egress from the ANC.
Activators of receptor-coupled guanylate cyclase (GC) Donors of Nitric oxide (NO) Direct activators of soluble guanylate cyclase	Natriuretic peptides and constrained cyclic peptides: CNP; TAK-639 NCX-125; (S)-nitrosoacetylpenicillamine; Sodium nitroprusside; Hydralazine; 3-morpholinosyndnonimine; MGV354; IWP-953;	The receptor-linked GC generates cGMP to relax TM and thus promote efflux of AQH from the ANC. The NO released from donor molecules generates cGMP via intracellular GC activation to relax TM. Direct stimulation of cytosolic GC generates cGMP to relax TM and thus promote AQH egress from the ANC.
Agonists of κ-opioid receptors	Dynorphin, Bremazocine	Have indirect effect through releasing natriuretic peptides which activate receptor-coupled GC to generate cGMP which relaxes TM to lower IOP.
Agonists of cannabinoid receptors	SR141716A; CP55940; WIN55212-2	These compounds are believed to stimulate K^+-channels which relaxes TM to promote AQH egress via TM/SC.
Inhibitors of autotaxin/ lysophosphatidic acid pathways	Aiprenon	The exact mode of action is not fully understood but appears to be activation of the TM/SC pathway of AQH outflow.
Stimulators of Uveoslceral Outflow of AQH		
Agonists of EP_2- and EP_4- PG-receptors	Butaprost; ONO-AE1-259-01; PF-04217329; AL-6598; PF-04475270; Omidenepag isopropyl (DE-117)	These compounds generate cAMP that relaxes CM and TM. Additionally, agonists at EP_2 receptors help degrade ECM within CM bundles and scleral tissue to help AQH leave the ANC via the UVSC outflow pathway.
Agonists of serotonin-2 (5HT-2) receptors	AL-34662; α-methyl-5HT; (R)-DOI;	These agonists contract/relax CM/TM to promote outflow of AQH. Additional IOP-lowering may be achieved via the UVSC pathway activation.
Agonists of bradykinin B_2-receptors	BKA278; FR-190997; Bradykinin	Stimulation of both TM/SC and UVSC outflow pathways to remove excess AQH from the ANC to help lower IOP. Cellular and molecular mechanisms involve PG and MMP release, and direct contraction/relaxation of CM/TM tissues.
Prostaglandin with dual activities	ONO-954, agonist at FP/EP3 receptors ()	AQH egress from ANC promoted via the UVSC outflow pathway
Purported inhibitors of AQH production		
Inhibitors of chloride channels	NPPB: 5-nitro-2-(3-phenyl-propyl-amino)-benzoate	Production of AQH is inhibited
Agonists of dopamine receptors	SDZ GLC-756; CHF1035; PD128907; CHF1024; 3-PPP ((S)-(−)-3-hydroxyphenyl)-N-n-propylpiperidine) ()	AQH generation is inhibited through blockade of norepinephrine release
Inhibitors of Na^+-K^+-ATPase	Digoxin analogs; Ouabain;	AQH generation is inhibited by blockade of this enzyme
Inhibitors of Aquaporin channels	Dihydrobenzofurans and aromatic sulfonamides	AQH generation is inhibited through blockade of norepinephrine release
Other Ocular hypotensive compounds		
Mas receptor stimulator Antagonists of angiotensin-II receptors	ACE-2 activation with DIZE CS-088	Possibly by reducing the accumulation of collagen and fibronectin in the TM area Weakly active ocular hypotensives with various proposed modes of action
Inhibitors of Ca^{2+}-channels	Iganidipine; Lomerazine; Nifedipine; Nivaldipine; Verapamil; Nimodipine; Brovincamine	Weak IOP-lowering activity
Antagonists of alpha-adrenergic receptors	5-methylurapidil; Oxymetazoline; Ketanserin	Purported IOP-lowering by AQH egress from ANC via TM/SC pathway
Activators of ATP-sensitive K^+-channels	CKPL1; Levocromakalim; Cromakalim	Work by lowering episcleral veinous pressure

start where herpes viral vectors were used (Kaufman et al., 1999). Rapid progression in development of safer and efficacious adenoviral vectors (AAV) and their deployment heralded a revolutionary success in use of intracameral gene therapy in a sheep model of steroid-induced glaucoma when glucocorticoid-inducible AVV carrying a human MMP-1 lowered IOP by 70% without too many overt side-effects such as ocular inflammation (Gerometta et al., 2010). Another elegant study demonstrated that lentiviral vectors could stably express cyclooxygenase-2, and when combined with an optimized synthetic FP-receptor transgene, successfully reduced IOP in the cat (Barraza et al., 2010). Similarly, in view of several genetic components to the etiology of ocular hypertension and POAG (Aung and Khor, 2016; Choquet et al., 2020) AVV-mediated delivery of exogenous TGF-β in rats resulted in elevation of IOP, thereby confirming the detrimental effects of this cytokine which causes deposition of excessive ECM within the TM/SC region to cause ocular hypertension (Robertson et al., 2010; Pfeiffer et al., 2017). From a therapeutic angle, genetic manipulations such as delivery of genes to corneal endothelial cells or ciliary body cells to release MMPs to help digest ECM to promote AQH egress from the anterior segment (O'Callaghan et al., 2017; Wu et al., 2020) and to silence beta-adrenergic receptors in the ciliary body with siRNAs to reduce AQH production (Moreno-Montañés et al., 2014) to lower IOP have also proven successful in rodent models of glaucoma. Similarly, knock-out of genes that hinder protection of RGCs or axonal/neurite elongation were deemed beneficial in animal models of GON (Huang et al., 2017; Mak et al., 2020). From a neuroprotection perspective, delivery of neurotrophin genes and its receptor protein to damaged or dying RGCs in order to preserve them and reduce vision loss also appears very promising for preserving vision in glaucoma suspects and in patients suffering from POAG/NTG (Khatib and Martin, 2017; Khatib et al., 2021). More recently, self-complementary AAV2 encoding a complement C3 protein, a destructive RGC attack and cell death-causing element, intravitreally delivered in rats protected the RGCs when the animals were subjected to ischemia/reperfusion-induced retinal injury (Tan et al., 2021). Similarly, delivery of gene therapy for the X-linked inhibitor of apoptosis (Visuvanathan et al., 2022) and BCLX, the endogenous antagonist of BAX (a damaging transcription factor that causing apoptosis) (Donahue et al., 2021), afforded protection and preservation of RGC cell structure and function two different rodent models of glaucoma. Thus, even though gene therapy appears a viable treatment modality for glaucoma, many challenges remain in translating such animal-based results to the human glaucomatous conditions (Amador et al., 2022; Ramlogan-Steel et al., 2019; Rhee and Shih, 2021). Likewise, use of CRISPR technology to edit specific genes also been accomplished in animals (Wu et al., 2020) and now requires to be demonstrated in human subjects in the future.

4.7. Cell therapy to combat GON

As discussed above, the natural senescence of TM cells in the anterior segment and demise of RGCs in the posterior segment of the eye due to aging and due to numerous chemical, mechanical and inflammatory insults during the development of ocular hypertension/POAG are now well accepted. Hence, it seems obvious that replacement of, and structural and functional integration of exogenously delivered cells or other components of would be helpful. However, there are many hurdles to overcome including the fact that when cells are injected as monodispersed entities, they still aggregate *in vivo*, and even if the cells were to remain singular, their correct integration into the existing architecture of the host retina and long-term viability is unassured. Additionally, there's no guarantee that the new cells will produce and secrete the necessary growth factors and other nutrients, generate new axons and have these connect to the requisite recipient thalamic neurons, and function as the original lost RGCs. Despite these issues, such a treatment paradigm has been attempted in animals with some level of success (Johnson and Martin, 2013; Abu-Hassan et al., 2015; Smedowski et al., 2016; Zhu et al., 2016, 2017, 2021). Similarly, use of stem cells to repair or replace TM cells in the anterior segment of the eye (Abu-Hassan et al., 2015; Yun et al., 2018; Zhu et al., 2016, 2017, 2021), and intravitreally delivered induced pluripotent stem cell-derived RGCs and/or Muller glia cells for potential transplantation into damaged retinas (Chamling et al., 2016; Harrell et al., 2019; Eastlake et al., 2021) or delivery of Schwann cells to compromised optic nerves of animals and humans could be exploited for repairing the structural elements of the retina-brain axis (Li et al., 2004; Hu et al., 2005; Fang et al., 2010; Guo et al., 2014; Smedowski et al., 2016). Again, *in vivo* translatability in multiple animal models of glaucoma/neurodegeneration and in different global research units, and eventual clinical applications with appropriate effectiveness need to be demonstrated. However, we await such exciting developments and peer-reviewed publications of the new research data.

4.8. Exosomes and miRNAs in POAG therapy

The traditional chemical communication between cells with hormones and neurotransmitters (Sharif et al., 2014; Sharif, 2018a; Bagher et al., 2018) has recently been superseded by the findings that cells also use nanotubes (Keller et al., 2017; Sun et al., 2019), and various types of nano- and micro-meter sized extracellular vesicles (Mead et al., 2018; Seyedrazizadeh et al., 2020) to deliver specific genetic (e.g. miRNAs) and/or neurotrophic agents (e.g. brain-derived growth factor) packaged within exosomes/secretomes (Valadi et al., 2007; Moss et al., 2021; Fayazi et al., 2021). Indeed, a recent report has described mouse retinal pericyte dysfunction and loss of interpericyte tunneling nanotubes being responsible for neurovascular problems in glaucoma (Alarcon-Martinez et al., 2022), thus confirming the previously proposed link between poor ocular blood flow and glaucoma, especially in NTG patients (Mozaffarieh and Flammer, 2013). The future appears bright if and when the application of such findings and technologies in a clinical setting for combating POAG/NTG can come to fruition.

4.9. Optogenetic treatment options for POAG/NTG and treatments for NAION

A combination of light or other forms of electromagnetic wave technology and genetics offer an innovative tool to achieve a gain of function in patients that are experiencing visual deficits due to chronic ocular hypertension/POAG/NTG. Indeed, optogenetic prosthesis and photoelectric dyes are in experimental trials not only for treatment of retinitis pigmentosa (Marc et al., 2014; Tochitsky and Kramer, 2015), but could be applied to patients with other retinal diseases such as POAG/NTG to help improve visual outcomes.

Even though no treatments exist for the sudden onset of NAION, there is new hope as suggested by some recent experimental approaches. Historically, even though intravitreal PGJ2 and a topically administered adenosine receptor agonist protected RGCs in rodent and monkey models of NAION they failed to promote functional recovery. This deficit has recently been overcome using a decoy NOGO-receptor blocking antibody (Wang et al., 2015), and with an antibody that sequestered NOGO and which reduced local inflammation and preserved RGCs and optic nerve structure and function (Johnson et al., 2021).

5. Conclusions

The prevalence of the insidious silent thief of eyesight, glaucoma, is increasing worldwide as more and more people are diagnosed and become patients for treatment. It is gratifying that a number of IOP-lowering drugs and combination products, surgical and implantable AQH-drainage devices technologies are available to help preserve vision in patients that suffer from chronic ocular hypertension, POAG and NTG and other forms of GON. There also exists great potential for other treatment modalities discussed above to be introduced into medical management of the latter eye diseases. It is hoped that continued

research and development efforts will yield suitable products to help combat such maladies in the near future.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.crneur.2022.100037.

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