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Review

Neuropathology and Therapeutics Addressing Glaucoma, a Prevalent Retina-Optic Nerve-Brain Disease that Causes Eyesight Impairment and Blindness

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Abstract

Glaucomatous optic neuropathy (GON) associated with different forms of glaucoma and chronic ocular hypertension (cOHT) is characterized by progressive loss of retinal ganglion cells and their axons in the optic nerves that project to the brain to transmit visual information. The resultant thinning of the optic nerves cause loss of peripheral vision, which if not halted or slowed, can lead to irreversible blindness. Whilst the precise triggering insult(s) for the primary open angle glaucoma (POAG), the most prevalent of the glaucomas, remains unknown, the most prominent risk factors include elevated intraocular pressure, increasing

age, African-American heritage (genetic predisposition), family history, low cerebral spinal/intracranial pressure, and vascular dysfunctions within the retina. However, whilst reduction of IOP by topical ocularly administered medications is the first-line therapeutic approach to address cOHT / POAG, surgical procedures and aqueous humor drainage devices are also useful means to lower IOP. It is hoped that the intense research into mechanisms underlying neurodegeneration has the potential to lead to discovery of potential neuroprotective and neuroregenerative agents s and technologies including novel sustained drug delivery platforms, gene therapy, cell therapy, physical support systems, food-derived nutrient treatments, neurostimulation via optogenetic, electrical and sonogenetic tools, yielding suitable treatments to treat cOHT / POAG and the attendant GON.

Keywords
Glaucoma; ocular hypertension; glaucomatous optic neuropathy; AQH drainage device; optic nerve degeneration; optic nerve head; retinal ganglion cells; nerve regeneration; neuroprotection

1. Introduction to the Eye and Visual System

As windows for the brain and providing vision, our eyes have a special place amongst the many organs within our bodies. Of the five senses, loss of sight is perceived as one of the most devastating and sorrowful event in the lives of those who experience such an unfortunate fate. Thus, preservation of vision is an extremely important and noble goal for mankind. The eye is indeed a very special organ with a complex structure composed of diverse cell-types with specific functions in the visual system (Figure 1A). At a gross level, compartmentalized into the anterior chamber (ANC) and posterior chamber (PSC) divided by the lens, the fluids within each segment are also unique with a watery nutritive fluid (aqueous humor; AQH [1]) bathing the ANC and a gelatinous material (vitreous humor) existing in the PSC. While cells lining the ANC are nourished by the AQH, a retinal blood supply provides nutrients to the retinal cells and which also removes metabolites and other substances from the retina, a very active energy-utilizing tissue. In that respect, the trabecular meshwork (TM) system [2-5], which is connected to the Schlemm's canal (SC; [6-8]) which empties the AQH into the veinous circulation, is also an active tissue that filters the AQH and digests debris present in the AQH (Figure 1B). This activity helps maintain a homeostatic environment which permits the eyeball to retain a constant shape such that the clarity of the AQH provides light a clear unobstructed path to reach the lens and be focused onto the retina [9]. Obviously, any event or factor that compromises the normal functions of the TM and those of the various retinal cells and the optic nerve poses grave consequences for the visual system. Indeed, TM dysfunction causes chronic ocular hypertension (cOHT; [9]) and damages ganglion cells (which are of different types depending on their receptive field, dendritic branching and conduction velocities [10, 11]) and their axons (that form the optic nerve [12]) through mechanical stretching and disruption of retinal tissue at the back of the eye which eventually leads to damage of retinal-optic nerve-brain connections resulting in various degrees of visual impairment.

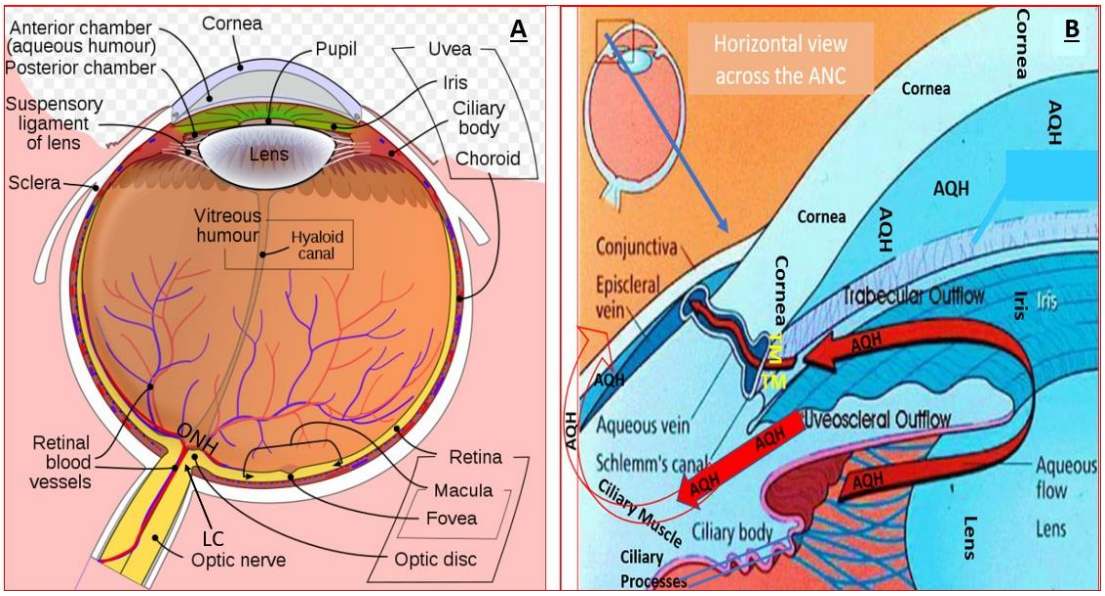

Figure 1 Anatomical location of various ocular tissues of the human eye are shown (A). AQH production and drainage from the anterior chamber of the eye via the conventional outflow pathway (via TM) and the uveoscleral (UVSC) pathway are also depicted (B).

Many specialized cells make up the retina including retinal ganglion cells (RGCs) [10, 11], interneurons (e.g. amacrine cells, horizontal cells and bipolar cells), Muller glia, photoreceptors (rods and cones), and retinal pigmented epithelial (RPE) cells (Figure 2A, Figure 2B). At the back of the eye, RPE cells lie adjacent to an outer limiting Bruch's membrane that separates the capillaries of the choroidal circulation from the RPE cells. At the anterior end of the retinal tissue is the inner limiting membrane that seperates the RGC axons from the vitreous humor (Figure 2B). Bundles of unmyelinated axons of RGCs, that form the retinal nerve fiber layer (RNFL) [13], gather from both sides of the retina towards the mid-line. The axon bundles make a 90-degree turn towards the back of the eye and make an exit from the eye at a site called the optic nerve head (ONH [13, 14]). As these axons traverse the width of the retina they pass through a honey-combed structure, lamina cribosa (LC) (Figure 1A, Figure 2B [15-17]), and eventually become parts of the optic nerve. In order to optimally conduct the electrical signals generated by the RGCs, their axons are myelinated when they are bundled together to form the optic nerves as they exit the back of the eyeball. The optic nerves cross over at the optic chiasm to innervate the thalamic, pre-tectal and suprachiasmatic nuclei of the contralateral sides of the brain [18, 19]. From there, relay axons project to different layers of the visual cortex [20] which are responsible for decoding the electrical signals from the RGCs for visual perception of the objects bein seen by the eyes (Figure 3).

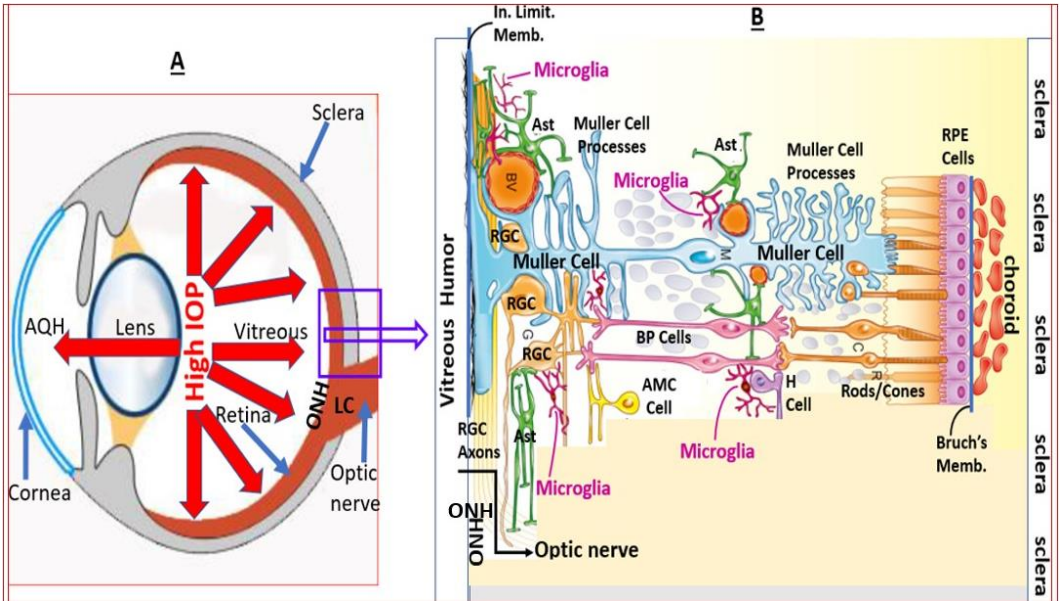

Figure 2 The elevated IOP-induced mechanical distortion affects all part of the eye and detrimentally impacts the back of the eye structures (A). In particular, the RGCs are injured through activation of resident and invading microglia (B) which release numerous toxic substances such as cytokines, glutamate, NO and endothelin. Note: these events do not necessarily occur sequentially. Also, since numerous types of RGCs exist with different levels of sensitivity to the toxins, not all RGCs are equally affected. Many types of interneurons in the retina are also subject to injury and damage by the deleterious factors in the extracellular space.

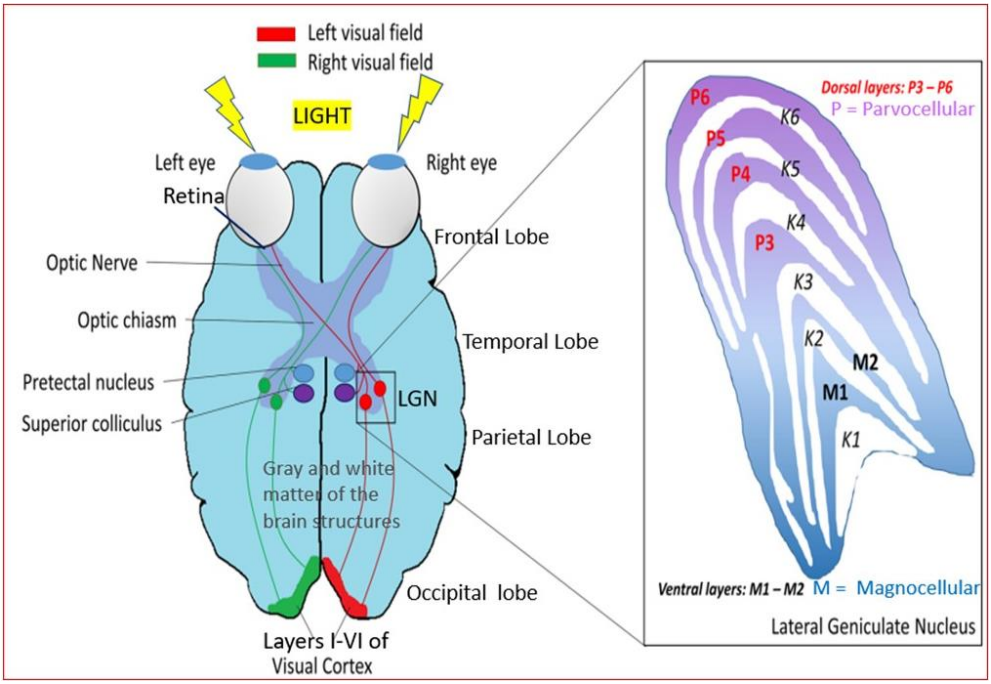

Figure 3 This schematic illustrates as a top-view of the components of the visual system encompassing the eye, retina, optic nerves, thalamic and cortical connections. The various layers of the lateral geniculate nuclei (LGN) composed of the parvocellular and magnocellular cells are depicted in the inset.

2. Retinal and Brain Involvement in Visual Processes and Vision Loss

Retinal photoreceptor initate the process of vision, once light hits the eye by converting light to electrical impulses by a hyperpolarization response. At a high-level, a cascade of neurotransmitters are released amongst the retinal cells and neurons whose interactions with specific pre- and post-synaptic receptors initiate a multitude of biochemical and electrical signals. These are progressively relayed to the RGCs which code the visual information and transmit to the brain via the optic nerve. Signal transmission from the retina to the brain occurs in approximately 0.15 seconds, and information transfer happens at roughly 10 million bits per second and vision occurs. This makes the retina and the brain extremely high energy-consuming tissues. Specificity of the visual signals reside in the different types of RGCs that exist in the retina and to the many different neurons in different layers of the lateral geniculate nuclei (LGN) (Figure 3), superior colliculus (SC), pretectal and suprachiasmatic nuclei (SCN), and of course the many different nuclei within the many layers of the visual cortex [18-20]. Cells within the LGN and visual cortical layers have specialized functions that code information according to color, shape, contrast, resolution, movement, etc. Furthermore, these many structures receive and send out signals to other important brain regions such as cerebellum, hippocampus and striatum, thereby permitting further modulatory actions on the visual processes and the ultimate image processing and perception by the person.

Specifically, most optic nerve terminals project to specific neurons within the LGN which sorts retinal signals into parallel streams comprised of color, structure, motion and contrast. The top four parvocellular layers of LGN handle color and resolution, while the bottom two magnocellular layers process contrast and motion (Figure 4). The corresponding primary visual cortex (PVC) is also highly organized to receive LGN inputs from their long axons to maintain fidelity and complexity of the image information. Direct mapping of RGCs is precisely imprinted in the PVC on a point-by-point basis in a columnar pattern of connections alternating between the left and right eyes that places objects perceptually in the horizontal and vertical axes. Rapid comparison of the binocular signal inputs by V1-PVC cells allows perception of depth of vision and hence objects appear in three-dimensions. As V1 cells sharpen the lines and edges of images, the cells of V2 region of PVC refines their coloration. Visual perception encompassing form and color in V3 and V4 regions of PVC, recognition of face and object in the inferior temporal lobe, and motion and spatial awareness covered by the parietal lobe of the cortex completes the overall visual picture of the objects being viewed by the person. This is a highly simplified summary of a very intricate visual system and the processes involved in visual perception, and it is hoped that it is sufficient for the current contextual purpose (Figure 4).

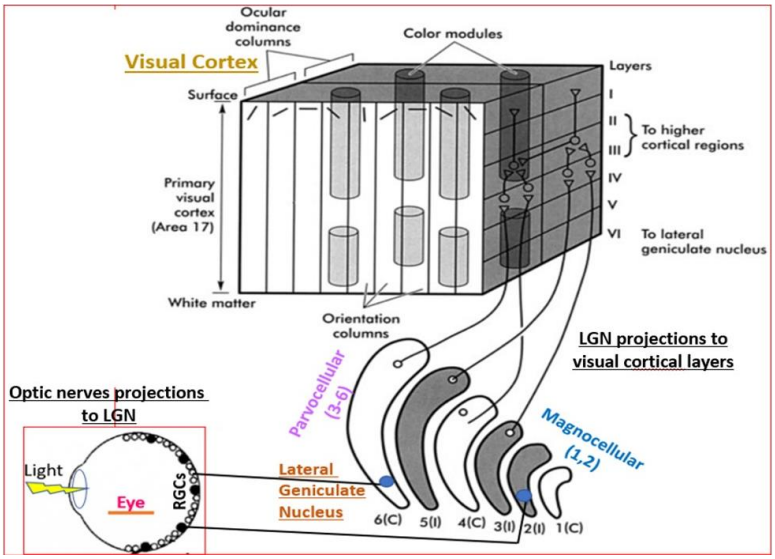

Figure 4 A high-level representation of the RGC-LGN-primary visual cortical layers and the related connections are shown in this diagram. The specificity of the connections covering color, contrast and resolution of images as perceived by the visual cortex neurons is described in more detail in the text.

3. Primary Open-Angle Glaucoma (POAG): Molecular and Cellular Pathology in the Retina-Optic Nerve-Brain Axis

The second leading cause of blindness worldwide is primary open-angle glaucoma (POAG) [21-24] which is often associated with abnormally and chronically high intraocular pressure (IOP) [21-24], and spontaneous IOP spikes [25], which is in turn caused by accumulation of excess AQH in the ANC of the eye [9, 21, 24]. AQH retention in the ANC primarily follows after deposition of aberrant collagen, fibronectin and extracellular matrix [26-30] in and adjacent to the TM, where TM cells that are susceptible to stress [31-33] and which have reduced capacity to phagocytose and digest such debris are killed [34]. Additional reduction and/or loss of autophagic mechanisms of TM cells [3, 4, 9, 34] exacerbate the situation causing further elevation of IOP [21-24]. This elevated IOP (Figure 2A), coupled with low intracranial fluid pressure (ICFP) [35-38] leads to constriction of the RGC axons at the LC [39] which damages the unmyelinated part of the optic nerve at the ONH and LC. Increasing evidence indicates that the LC/ONH regions of the retina which are negatively impacted by the high IOP [13, 14, 40] and the RGC axons there are assaulted by a range of locally released inflammatory cytokines (e.g. tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6) due to inflammasome activation [41-46], and by other cytotoxic substances (e.g. glutamate [47-51], ATP [52], nitric oxide [53-57], endothelin [58-60], amyloid-β (AM-β) [61, 62], phosphorylated-Tau [pTau]) and matrix metalloproteinases (MMPs) and other proteases [63, 64] that degrade the structural matrix of the ONH and LC (Figure 5, Figure 6) [63, 64]. Such damage severely reduces the strength and integrity of the RGC axons and the surrounding ECM holding them in place, and where lipofuscin [15, 65] accumulate. Again, dysfunctional autophagic processes [19, 66], at the ONH/LC regions allow cellular debris to accumulate resulting in scar formation. which leads to bending and stretching of the overall optic nerves resulting in atrophy and shrinkage of the RGC axons, reduction in axonal flow of mitochondria to the RGCs, and thus reduced energy production [67-71] to maintain cellular functions within the RGC somas], and reduced transport of vital growth factors [72-75] to the RGC

bodies and ultimate RGC senescence. Thus, many potential sites of damage within the brain-optic nerve-retina visual system exist involving multiple deleterious neurotoxic and neuroinflammatory molecules and processes [76-82], reduced cerebral and retinal blood-flow [83, 84], and abnormally diminished cerebral spinal/intracranial pressure [35-39] (Figure 5, Figure 6).

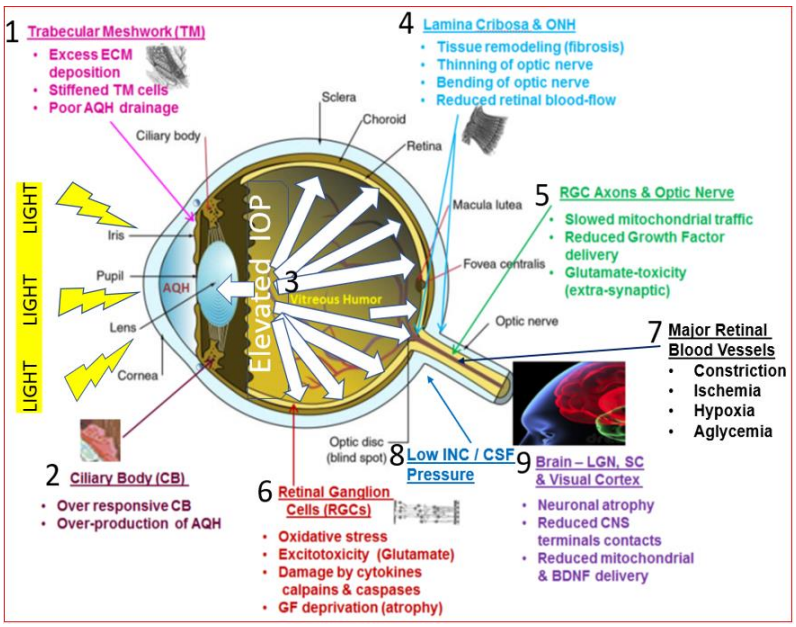

Figure 5 The various loci of damage and the different insults and factors involved in causing cOHT/POAG resulting in GON are indicated in this schematic. Many of the inflammatory, immunologic and degenerative processes probably occur simultaneously but may last over different periods of time.

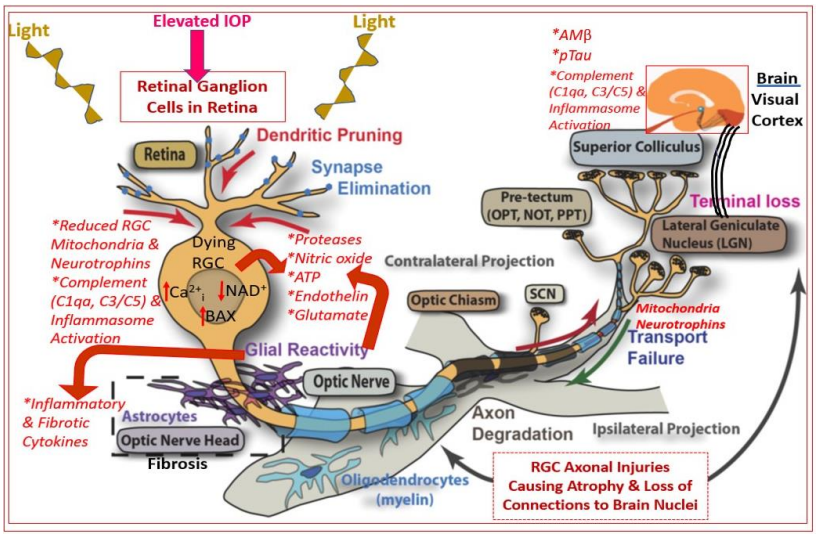

Figure 6 This cartoon shows the multitude of events and damaging molecules involved in causing injury and death of RGCs, RGC axons and their terminals in the brain structures during the course of chronic OHT / POAG / NTG. Due to the heterogeneity of the RGCs and differential susceptibility and sensitivity to physical pressure and toxic agents, it is likely that not all patients will experience the same degree of visual impairment and their disease progression will also differ.

The cascade of damaging events described above, some happening sequentially and some in parallel, are responsible for the loss of many vulnerable RGCs and their axons [85-90]. The net result is reduced transmission of visual signals to the brain. Since the brain structures are reliant on electrical activity from the retina to also remain healthy, death signals from the RGC axons due to POAG/ GON may cause senolytic events in the thalamic and visual cortical tissues due to inducted neuroinflammation [91]. Apoptotic and neurodegenerative processes lead to death of neurons in the LGN, magnocellular and parvocellular layers of the thalamus [92-96], trans-neuronal degeneration and extensive brain network reorganization and disruption [97-100] culminating in reduction of visual acuity (including reduced contrast sensitivity), visual impairment (loss of peripheral vision), and if left undiagnosed and untreated, loss of central vision followed by total blindness.

What is disturbing to the POAG patient, and also to those patients with relatively normal IOPs (normotensive glaucoma [NTG]) [101-105], is that the disease is imperceptible, painless and continues unabated for multiple decades. Due to neuroplasticity, early defects in the retina-optic nerve-brain system are somewhat compensated and perception of suprathreshold contrast in patient's vision is maintained despite loss of some visual sensitivity [106]. Patients first become aware of their POAG/NTG when their peripheral vision is reduced, black patches randomly intrude into their line of sight, and when this progresses over many decades to "tunnel vision" [107]. These insidious changes in visual perception indicate that now the tipping point has been reached and in fact 400,000 to 600,000 RGCs have been destroyed from the patient's retina and an equal number of connections to the brain have been silenced. Hence, early diagnosis through regular eye exams is tantamount to receiving treatment close to the time of disease initiation and perhaps slowing down the demise of RGCs and thus reducing disease progression. Sadly, it is estimated that 53-58 million people will be afflicted with POAG by 2040 with the total glaucoma patient population reaching ~112 million by 2040 [108, 109]. Therefore, there is an urgent need to diagnose patients at risk of chronic OHT (cOHT) / POAG earlier and discover and bring to the clinic novel IOP-lowering drugs and treatments that offer greater potency/efficacy and longer duration of action with a reduced side-effects profile to existing therapies. Furthermore, it is now well accepted that IOP reduction alone is insufficient to prevent visual defects in POAG/NTG, such that we need to directly protect the RGCs and their axons through some innovative rescue strategies. In addition to neuroprotection strategies to enhance the survival of RGCs, there is a need to repair RGC axons in order to more fully re-establish retino-thalamic connections. Clearly, GON being a multifactorial optic/brain disease will require a multifaceted treatment approach and these elements will be discussed below.

4. Treatment Options for cOHT / POAG: Drugs, Surgeries and AQH Microshunts

With advancing age and/or due to many other disease-initiating processes including loss of TM cells due to natural or abnormal senescence caused by endoplasmic reticular stress, poor autophagy, reduced phagocytic performance of remaining TM cells, the conventional AQH drainage system gets overwhelmed by the accumulating debris and becomes clogged [3, 6]. Since the ciliary bodies continue to produce fresh AQH, the anterior chamber of the eye begins to expand and bulge thereby raising the IOP. This elevated IOP is transmitted through the eye and negatively impacts the weakest part of the visual system, the LC that lies just behind the ONH [13, 14, 19, 45] where the

unmyelinated axons of the RGCs gather and exit the back of the eye to form the optic nerve. This then initiates the detrimental cascade of events mentioned in the previous section above leading to visual impairment [91, 94, 98]. Clearly opening up of the TM outflow pathway and engaging the other non-conventional uveoscleral pathway would relieve some damaging effects of the raised IOP. To this end, numerous pharmaceutical drugs that reduce AQH formation (carbonic anhydrase inhibitors (e.g. dorzolamide; [110]), alpha-2-adrenergic agonists (e.g. brimonidine; [111]), beta-blockers (e.g. timolol and betaxolol; [112])), and those drugs that primarily promote AQH efflux via the conventional TM/SC outflow pathway (muscarinic agonists (e.g. pilocarpine; [113]); rho kinase inhibitors (e.g. ripasudil, netarsudil; [114, 115]), and drugs that primarily stimulate AQH outflow via the uveoscleral pathway (prostaglandin (PG) FP-receptor agonists (e.g. latanoprost, travoprost and tafluprost; [116-118]), a novel non-PG EP2-receptor agonist (omidenepag isopropyl; [119-123]), and a conjugate of latanoprost and an nitric oxide releasing molecule (latanoprostene; [124])) have been discovered, developed and introduced into the clinical management of OHT / POAG (Table 1). The duality of mechanism of action of FP-PG agonists such as travoprost [117] and that of the non-PG EP2-receptor agonist, omidenepag isopropyl [120], inducing outflow of AQH via the uveoscleral and TM/SC pathways seems unique. Interestingly, the other unique property pertains to the rho kinase inhibitor, netarsudil, which lower IOP by stimulating AQH outflow via the TM/SC and by lowering episcleral veinous pressure in animals and human OHT/POAG patients [125, 126]. Additionally, since netarsudil and omidenepag isopropyl lower IOP well in normotensive and OHT animals, they may have clinical utility in treating NTG. However, this remains to be demonstrated in additional clinical studies.

Table 1 Health agency-approved medications for treatment of cOHT / POAG / NTG.

Branded medication & year of health agency approval	Generic name and class of compound	Dosage and formulation available (%, w/v)	Recommended frequency of topical ocular administration	Mode of action to reduce IOP	Key side-effects noted
First-Line Treatment Drugs: Stimulators of UVSC Outflow of AQH to lower IOP					
Xalatan (USA FDA approved; 1996)	Latanoprost (Free acid is a relatively selective agonist of the FP-prostaglandin receptors).	0.005% solution	1 topical ocular eyedrop at bedtime	Promotes 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 thickening and lengthening, periorbital fat loss resulting in "sunken eyes look", eyelid discomfort due to crusting, and photophobia.
Travatan (USA FDA approved; 2001)	Travoprost (Free acid is a highly selective agonist of the FP-prostaglandin receptors).	0.004% solution	1 topical ocular eyedrop at bedtime	Promotes 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 FDA approved; 2001)	Bimatoprost (Free acid is a relatively	0.03% solution	1 topical ocular eyedrop at bedtime	Promotes AQH egress via UVSC and TM/SC routes of drainage	Conjunctival redness, uneven thickening and elongation of eyelashes, iris darkening,

	selective agonist of the FP-prostaglandin receptors).				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 PMDA approved; 2008) Zioptan (USA FDA approved; 2012)	Tafluprost (Free acid is a Relatively selective agonist of the FP-prostaglandin receptors).	0.0015% solution	1 topical ocular eyedrop at bedtime	Promotes 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 FDA approved; 2000)	Unoprostone (free acid is a weak partial agonist at the FP-receptor)	0.15% solution	1 topical ocular eyedrop twice/day	Weakly Promotes 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 PMDA approved; 2018)	Omidenepag Isopropyl (Free acid is a non-prostaglandin EP2-receptor selective agonist)	0.002% solution	1 topical ocular eyedrop/day	Promotes AQH outflow via both UVSC and TM/SC pathways.	Major ocular side-effects are transient redness of the conjunctiva and corneal thickening.
Stimulators of AQH outflow via the conventional outflow (TM/SC) pathway					
Isopto carpine (USA FDA approved; 1974); Pilopine	Pilocarpine (Agonist at muscarinic receptors; mostly M1)	1%, 2%, 4%; and as 4% Gel	1 topical ocular drop ranging from 2-4-times /day and 1 application of gel across the eye	Promotion 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)	1.5% and 3% solutions	1-2 topical ocular drops up to 3-times on a daily basis	Promotion 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 (Japanese PMDA approved; 2014)	Ripasudil (Inhibitor of Rho kinase [ROCK]) (3.5-4.5 mmHg IOP lowering achieved)	0.4% solution	1-2 topical ocular drops /day	Promotion of AQH drainage via TM /SC route	Conjunctival irritation and allergic reaction, punctate keratitis and blepharitis

Rhopressa (USA FDA approved; 2017)	Netarsudil (Inhibitor of Rho kinase [ROCK]) (5 mmHg IOP reduction)	0.02% solution	1 topical ocular drop /day	Promotion of AQH drainage via TM/SC route; also lowers episcleral veinous pressure	Ocular redness, ocular pain, hemorrhage of conjunctival blood vessels, verticillata of cornea.
Inflow inhibitor drugs: AQH production inhibitors					
Timoptic (USA FDA approved; 1978) Timoptic-XE Gel	Timolol (Antagonist of beta-adrenoceptors in CB)	0.25%, 0.5% solutions or as a gel-forming formulation	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 FDA approved; 1985)	Betaxolol (Antagonist of beta-1-adrenoceptors)	0.25% suspension and a 0.5% solution	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, pulmonary distress, asthma and respiratory issues, insomnia, lethargy, depression, headache, dizziness.

Alphagan (USA FDA approved; 1996)	Brimonidine (IOP reduced by 2-6 mmHg)	0.15% and 0.2% solutions	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 FDA approved; 1987)	Apraclonidine	0.5% solution	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.
Trusopt (USA FDA approved; 1994)	Dorzolamide (Inhibitor of carbonic anhydrase)	2% solution	1 topical ocular drop 3-times/day	Inhibition of AQH production from CB	Ocular itch, tearing, eye discharge, ocular irritation, blurred vision, hyperemia, clumsiness, depression, dizziness, irregular heartbeat, chest pain Eye irritation, burning, stinging, blurred vision, tearing, photophobia, superficial punctate keratitis, ocular

					surface dryness, transient bitter taste.
Azopt (USA FDA approved; 1998)	Brinzolamide (Inhibitor of carbonic anhydrase)	1% suspension formulation	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.
Fixed-Dose Combination Products Used to Treat cOHT/POAG/NTG					
Cosopt (USA FDA approved; 1998)	Dorzolamide & Timolol	Fixed dose (2% + 0.5%) formulation	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 FDA approved; 2007)	Brimonidine &Timolol	Fixed dose (0.2% + 0.5%) formulation	1 eyedrop every 12 hrs	Inhibition of AQH generation at CB level	Side-effects included those induced by each of the drugs administered alone (see above)
Simbrinza (USA FDA approved; 2013)	Brinzolamide & Brimonidine	Fixed dose (1% + 0.2%) formulation	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 FDA approved; 2019)	Netarsudil & Latanoprost	Fixed dose (0.02% + 0.005%) formulation	1 eyedrop/day	Promotion 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	Fixed dose (0.005% + 0.5%) formulation	1 eyedrop/day	Promotion 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	Fixed dose (0.004% + 0.5%) formulation	1 eyedrop/day	Promotion 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	Fixed dose (0.03% + 0.5%) formulation	1 eyedrop/day	Promotion 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)
Taflotan + Timolol	Taflotan & Timolol (IOP-lowering observed were >13 mmHg; 40% reduction)	fixed dose (0.0015% + 0.5%) formulation	1 eyedrop/day	Promotion 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)

Other IOP-lowering Products

Durysta Implant (USA FDA approved; 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.	Promotion 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.
Vyzulta (USA FDA approved; 2017)	Latanoprostene Bunod (This is a conjugate drug composed of latanoprost and a NO-donor molecule)	Fixed dose (0.024% solution) formulation	1 eyedrop at bedtime	Promotion 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.

Combinations of approved IOP-lowering medications, allowing engagement of multiple mechanisms of action to achieve higher efficacy, have also been developed for medical treatment of OHT/POAG [127, 128]. Furthermore, the durability of the ocular hypotensive activity of drugs has been extended using polymer-based technology that permits the drug to be released into the ANC over time once the polymer rod is intracamerally injected into the ANC [129, 130], or the drug is slowly eluted off from a silicon-ring-device placed around the eyeball and remains in contact with the conjunctiva/cornea [131], or the therapeutic drug is slowly released from punctal plugs [132], or via nanoparticles [133, 134], polycaprolactones [135, 136] or via port delivery systems akin to how antibodies are delivered to the eye [137]. Another recent important advent helping significantly lower and control IOP involves microshunts (e.g. Preserflo®) [138-142] which when placed into the ANC of the eye help drain the excess AQH to efficaciously lower IOP over many years, and improve visual acuity [140]. If needed, the patient can have the microshunt placed to drain the AQH and be treated topical ocularly with ocular hypotensive drugs to achieve the target IOP.

Even though the afore-mentioned therapeutic approaches tackle cOHT fairly well, new drugs with new mechanism(s) of action such as lowering IOP by decreasing episcleral venous pressure are needed. Similarly, lowering IOP through novel receptor or enzyme systems with a greater potency/efficacy and with lower side-effects potential [143, 144] than existing drugs are continuing to be found and developed for use in the clinical setting (Table 2). Progression of these novel ocular hypotensives drugs targeting many different receptors, enzymes, and ion-channels at the level of TM/SC and UVSC outflow pathways [145-169] into formal development processes is eagerly awaited.

Table 2 List of compounds that lower IOP in various animal models of acute or chronic OHT / POAG.

Classes of compounds	Names of tested compounds	Claimed or confirmed mechanism(s) of action
Stimulators of Uveoslceral Outflow of AQH		
Agonists of serotonin-2 (5HT-2) receptors	α-methyl-5HT; AL-34662; (R)-DOI	These compounds contract or relax CM/TM to stimulate outflow of AQH. Additional IOP-lowering may be achieved via the UVSC pathway activation.
Agonists of bradykinin B_2-receptors	FR-190997; BKA278; Bradykinin	Activation of both TM/SC and UVSC outflow mechanisms to eliminate AQH from the ANC occurs with these agonists. Cellular and molecular mechanisms involve PGs and MMPs release, and direct contraction / relaxation of CM/TM tissues.
Agonists of EP_2- and EP_4- PG-receptors	Butaprost; AL-6598; ONO-AE1-259-01; PF-4217329; PF-04475270	These agonists produce intracellular cAMP that relaxes CM and TM tissues. Additionally, agonists at EP_2 receptors help degrade ECM in CM bundles and

		sclera to promote AQH efflux from the ANC via the UVSC outflow route.
Prostaglandin with dual receptor activities	ONO-954, agonist at FP/EP3 receptors	Mainly stimulate AQH egress from ANC via the UVSC outflow pathway. Engagement of the TM/SC route of AQH efflux is also indicated.
TM/SC conventional outflow stimulators		
Tie-2 Activator, VE-PTP Inhibitor	Razuprotafib	Stabilizes SC /ocular lymphatic system to provide adjunctive AQH outflow via TM/SC pathway
Mas receptor (ACE-2) activator	Diminazene Aceturate (DIZE)	By reducing the accumulation of collagen and fibronectin in the TM area and enhancing AQH outflow.
Direct activators of intracellular soluble guanylate cyclase (GC)	IWP-953; MGV354;	Direct stimulation of cytosolic GC generates cGMP to relax TM and thus promote AQH egress from the ANC via the TM/SC pathway.
Activators of receptor-coupled guanylate cyclase	CNP; TAK-639;	The receptor-linked GC produces intracellular cGMP to relax TM and thus promote efflux of AQH from the ANC via TM/SC route.
Donors of Nitric oxide (NO)	NCX-125; (S)-nitrosoacetylpenicillamine; Sodium nitroprusside; Hydralazine; 3-morpholinosyndnonimine	The NO released from donor compounds generates cGMP via intracellular GC activation to promote relaxation of the TM.
Inhibitors of Rho kinase (ROCK)	First generation ROCK inhibitors include Fasudil and Y-27632. New ones include AMA0076 and ITRI-E-212.	These ROCK inhibitors possess some level of selectivity for rho kinase, and they cause relaxation of the TM to permit AQH efflux from the ANC to lower IOP.
Inhibitors of various kinases	Myosin-II ATPase inhibitor like blebbistatin. LIM-K inhibitors (e.g. LX7101); Staurosporin; Chelerythrine; Src kinase inhibitor	These compounds inhibit various kinases including ROCK-I and ROCK-II. These agents are less ROCK-selective and may produce more side-effects than selective ROCK inhibitors.
Agonists of cannabinoid receptors	WIN55212-2; SR141716A; CP55940;	These compounds are believed to stimulate K^+-channels which relaxes TM to promote AQH egress via TM/SC.
Inhibitors of transient receptor potential vanilloid 4 (TRPV4)-channels	GSK2193874; HC067047	Engagement of the conventional TM/SC pathway to cause IOP-lowering is indicated.

Inhibitors of autotaxin / lysophosphatidic acid pathway compounds	Aiprenon	Unknown mechanism of action although engagement of the conventional TM/SC pathway to cause IOP-lowering is indicated.
Cytoskeletal change inducers	Ethacrynic acid; Ticrynafen; Indacrinone	These agents interfere with actin-myosin mechanism to cause TM cell-shape changes to affect outflow of AQH. Some activity may be mediated via chloride transport inhibition.
Agonists of κ-opioid receptors	Bremazocine; Dynorphin	These agonists stimulate release of endogenous natriuretic peptides which activate receptor-coupled GC to generate cGMP, thereby causing TM relaxation and IOP-lowering.
Purported blockers of AQH production or water-channel inhibitors		
Inhibitors of aquaporin water-channels	Dihydrobenzofurans and aromatic sulfonamides	Water-channel blockade causes IOP-lowering.
Agonists of dopamine receptors	PD128907; SDZ GLC-756; CHF1035; CHF1024; 3-PPP ((S)-(-)-3-hydroxyphenyl)-N-n-propylpiperidine).	Inhibition of norepinephrine release causes less AQH production by the CB
Inhibitors of Na^+-K^+-ATPase	Ouabain; Digoxin analogs;	Inhibition of this ATPase reduces AQH production by the CB
Inhibitors of chloride channels	NPPB: 5-nitro-2-(3-phenyl-propyl-amino)-benzoate.	AQH generation by the CB is inhibited when Cl^--channels are blocked.
Additional agents that lower IOP		
Stimulators of ATP-sensitive K^+-channels	Cromakalim; CKPL1; Levocromakalim, QLS-101.	These compounds relax episcleral veinous blood vessels to lower IOP
Alpha-adrenergic receptors blockers	Oxymetazoline; 5-methylurapidil; Ketanserin	These antagonist compounds appear to lower IOP by stimulating TM/SC outflow of AQH
Ca^{2+}-channel inhibitors	Nimodipine; Lomerazine; Iganidipine ; Nifedipine; Nivaldipine; Verapamil; Brovincamine	May relax TM episcleral veinous blood vessels to weakly lower IOP.
Antagonist of angiotensin-II receptors	CS-088	Undefined; various proposed mechanisms of action

5. Treatments Beyond IOP-Lowering:

5.1 Cyto- and Neuro-protective Therapies

In view of the multiplicity of damaging and destructive factors involved in the etiology and progression of cOHT/ POAG / NTG (Figure 5, Figure 6), it seems obvious that a singular preventative regimen is unlikely to be very successful. Rather a combinatorial approach [170] is necessitated with multiple interventional points [171-176] involving IOP reduction coupled with slowing/preventing local inflammation at the ONH/LC. However, as the ANC components strongly influence the pathological events at the back of the eye, it is imperative that some rescue strategies be directed there. Thus, means to stimulate autophagic activity of TM cells thus reduce their stress due to ECM accumulation and delivery of anti-oxidants to the ANC would be helpful [177-182]. Likewise, since inflammation is a one of the root causes of RGC death and destruction of their axons and of the associated brain neurons, dampening or eliminating such destructive elements is beneficial [183-191]. Preventing complement activation [192] and up-regulating protective endogenous genes and transcription factors [193, 194] at the ONH/LC and thalamic and cortical regions is another useful strategy. Many other drugs and treatments [168, 195-204] including senolytic drugs [195], glutamate receptor antagonists [197], delta-opioids [198], histone deacetylase inhibitors [199], vascular-specific phosphatase blockers [168], alpha-2 adrenergic agonists [200], sigma-receptor agonists [201], and various neurotrophic factors [202, 203]. Furthermore, new conjugate/hybrid drugs with multi-pharmacophoric activities [205-210] directed at different intervention points of the RGC soma and axonal demise [170-176] are showing promise as neuroprotective agents.

5.2 Genetics, Cell Transplantation and Exosome-Based Therapies

Specific gene-therapy technologies are being utilized to curb the cyto-destructive and neurogenerative processes occurring during cOHT/POAG/GON. Some are addressing the reduced capacity of TM and other ANC cells to produce ECM-clearing MMPs [211] or modulating aquaporins to achieve AQH dynamic homeostasis [212]. Gene knock-out [213, 214] or gene insertion [215-217] to promote delivery of various trophic factors such as brain-derived neurotrophic factor and ciliary neurotrophic factor to RGCs [218, 219] that can rescue and preserve retinal and brain neurons are proving beneficial at least in animal models of POAG/GON. The advent and utility of cell replacement techniques and technologies to preserve retinal-optic nerve-brain connectivity and function involving stem cells for ANC pathologies [220-224], Schwann cells for optic nerve sheath replacement [225, 226] and for RGC and Muller transplantation [227-231] are gaining prominence. Additionally, the experimental utility of extracellular vesicles and/or use of stem-cell-derived exosomes and secretomes [232-235] comprising many different protective proteins and micro-RNAs impart beneficial effects on the many cell-types that are integrally involved in the visual processes. Eventually, structural bio-materials may be needed to physically support the optic nerves to halt and prevent further damage of these vital structures [236-239].

5.3 Dietary Factors Providing Cellular Protection

It is well known that food-derived nutrients possess a multitude of health-promoting chemicals that positively impact bodily muscles, bones and cells of many organs, including the eye [240-258].

In this respect, a whole host of nutraceuticals possessing antioxidant, anti-inflammatory, anti-excitotoxic, and anti-apoptotic properties protect RGCs and brain neurons, including curcumin, ginkgo bilboba, lipoic acid, coenzyme Q10, saffron, vitamin B3, and urolithin from pomegranates. Although somewhat controversial, recent research appears to link the dietary intake of foods with resident microbes in the alimentary canal and as such the latter influencing the disease pathology and thus potential protective properties of the microbiota [259]. However, whilst giving us hope and encouragement, confirmatory clinical trials of the nicotinamide alone [256] and in combination with pyruvate [257], and with the urolithin [258] are needed.

5.4 Axonal and Cellular Regeneration Therapies

There are many limitations of successfully delivering, uptake, incorporation and functional integration of food-derived nutrients, gene- and cell-therapies for the protection and preservation of eyesight of cOHT/POAG/NTG and GON sufferers. To overcome such hurdles, new ways to activate intrinsic cyto- and neuro-protective factors and systems are being explored. These include gross or cell-directed *in vitro* and *in vivo* electrical stimulatory systems and devices. Indeed, some success has already been realized in this arena where low-level electrotherapy has helped regenerate RGC axons, promote Muller cell proliferation/differentiation through release of endogenous neurotrophins and other beneficial substances [260-263]. Translation of these findings to the human situation appear promising [260, 263].

6. Novel Techniques and Technologies to Help Preserve Eyesight

As technologies progress, there is continuing hope that they would be applied to help glaucoma patients. Examples of these include the following: stem-cell-derived exosomal delivery of miRNAs and trophic factors [264-266], creation of artificial extracellular vesicles and stem cells with selective packaging of the cargos to be delivered [267, 268]. Moreover, use of novel cell repair and regeneration methods [269-278], use of optic nerve and visual field magnetic resonance imaging and mapping [279, 280] coupled with artificial intelligence technologies for earlier diagnosis of glaucoma [281, 282], functional retinal oximetry to determine the metabolic status of the retinal cells [283] and adaptive optics to improve the cellular resolution to detect structural changes at the cell soma and dendrites before and after treatment for glaucoma [284] will undoubtedly help glaucoma patients in the future. Much progress has also been achieved using optogenetic technologies to restore vision in animals [285-289], and using chemical photoswitches [285] and retinal and brain implants [285, 290]. Use of sonar technology to stimulate specific neuronal pathways to protect and enhance vision also holds great promise [291, 292].

The early and accurate detection and diagnosis of cOHT / POAG/ NTG is key to helping patients with visual impairment and as such 24-hr monitoring of IOP is essential. A contact lens-based IOP recording device has been developed to aid in this endeavor [293]. Fluid drainage via the traditional pathways from the eye are damaged during development of cOHT/POAG, and thus the ability to engage lymphatic drainage in the eye and brain may be useful [294, 295]. Similarly, development of new diagnostic/ biomarker techniques are critical for starting treatment to preserve and slow down GON, and recent reports are encouraging in this respect [296-299].

Use of single cell transcriptomics [300], anti-sense oligonucleotides [152], antibodies directed at inflammatory mediators [301], and use of specific micro-RNAs to lower IOP and perhaps provide

neuroprotection [149] by exploiting recently discovered cellular nanotubes [302] are exciting new developments worthy of further pursuit. Last but not least, novel imaging technologies using 2-photon-excited fluorescence and flood-illumination adaptive optics [303, 304], coupled with proteostasis drugs to eliminate excess phosphorylated proteins and misfolded proteins [305, 306] from the ANC and from the retina/optic nerve/brain offer new treatment paradigms for cOHT/POAG/NTG/GON, especially if the combinatorial treatments [257, 307] are reproduced in other clinical trials across the world.

7. Conclusions

Apart from causing visual impairment in the early stages of GON development, the disease progression robs patients of their ability to perform daily tasks such as reading, driving, and clearly recognizing objects and faces. These difficulties translate into various disabilities associated with visual field deterioration resulting in POAG patients bumping into objects-, falling down and sustaining injuries, and as the situation worsens can then cause anxiety and depression (Figure 7). Thankfully, as described above, significant progress has been made in the last dozen years towards a better understanding of the factors and pathologies involved in the GON disease processes endured by patients that suffer from cOHT / POAG/ NTG. Advancements in early and more accurate diagnosis of these ocular ailments is still lagging behind expectations although new biomarkers and devices hold great promise. The multifactorial nature of the damaging agents, insults and pathways involved in causing the sight-threatening diseases will certainly require a multicomponent treatment regimen. This will also necessitate varied permutations and combinations of drugs/devices/nutraceuticals/regenerative medicines designed to account for genetic, structural and functional elements impacted and experienced by each patient. Such personalized medicine will come to fruition in due course if we collectively continue to forge ahead discovering and developing new treatment modalities in a multidisciplinary manner to help the POAG/NTG patients preserve and protect their eyesight.

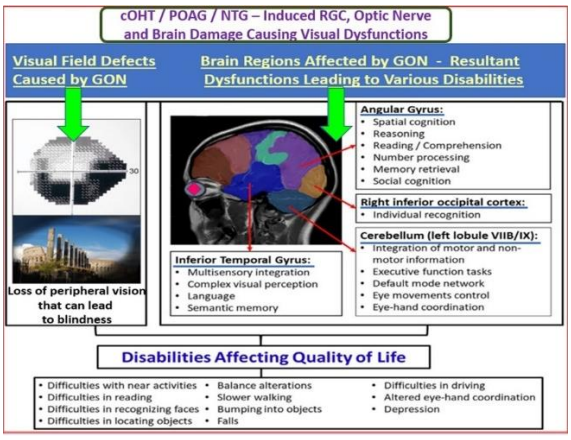

Figure 7 The negative impact of glaucomatous optic neuropathy as a result of cOHT / POAG causing visual field loss and various consequences of death of thalamic, cerebellar, and cortical neurons is highlighted in this schematic. Patients suffering from GON not only lose peripheral vision but also experience a whole host of other neurological disturbances which lowers their quality of life due to many types of disabilities listed in this figure.

Author Contributions

The author is solely responsible for conceptualizing, researching and writing this article.

Competing Interests

The author declares that there is no competing interest in writing this article. The only intention is to gather, collate and disseminate the high-level information about the pathological aspects of glaucoma and ocular hypertension with the hope that it will enhance multidisciplinary awareness about these sight threatening eye diseases. In time, I hope further research will be stimulated and innovation will lead to new and improved therapies for the patients who live with these ocular disorders.

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