



# Ocular Hypertension and Glaucoma: A Review and Current Perspectives

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**Abstract:** Hypertension of the eye fundamentally results from an imbalance between the production and extrusion of aqueous humor (AQH) within the anterior segment of the eye. Vitreous humor (VH) (in the posterior segment of the eye) and AQH are responsible for maintaining the shape of the eye-ball in order that light is correctly focused on the retina for good vision. However, as we age, cells of the AQH drainage system (trabecular meshwork, TM) die and cellular debris accumulates within the TM and the canal of Schlemm thereby slowing, and in some cases, preventing AQH efflux. This results in increased resistance and elevation of hydrostatic pressure within the anterior segment, also termed as elevated intraocular pressure (IOP) or ocular hypertension (OHT). Sustained OHT exerts mechanical pressure on the retinal ganglion cells (RGCs) and the optic nerve fibers at the back of the eye leading to their progressive demise by apoptosis, thereby distorting and diminishing visual acuity over time, and eventually leading to irreversible blindness. In some patients even “normal” IOP is destructive because their RGCs and their axons projecting to the brain are genetically or chemically predisposed to early cell death. These pathologies are termed “glaucomatous optic neuropathy (GON)” and OHT is often associated with glaucoma, especially primary open-angle glaucoma (POAG). Today, there are several pharmacological and minimally invasive surgical interventions / devices that constitute therapeutic modalities to treat OHT and glaucoma. OHT etiology and treatments will be discussed in more detail in this review article.

**Keywords:** Glaucoma, Ocular Hypertension, Neuroprotection, Pharmacology, Aqueous Humor

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## 1. Introduction

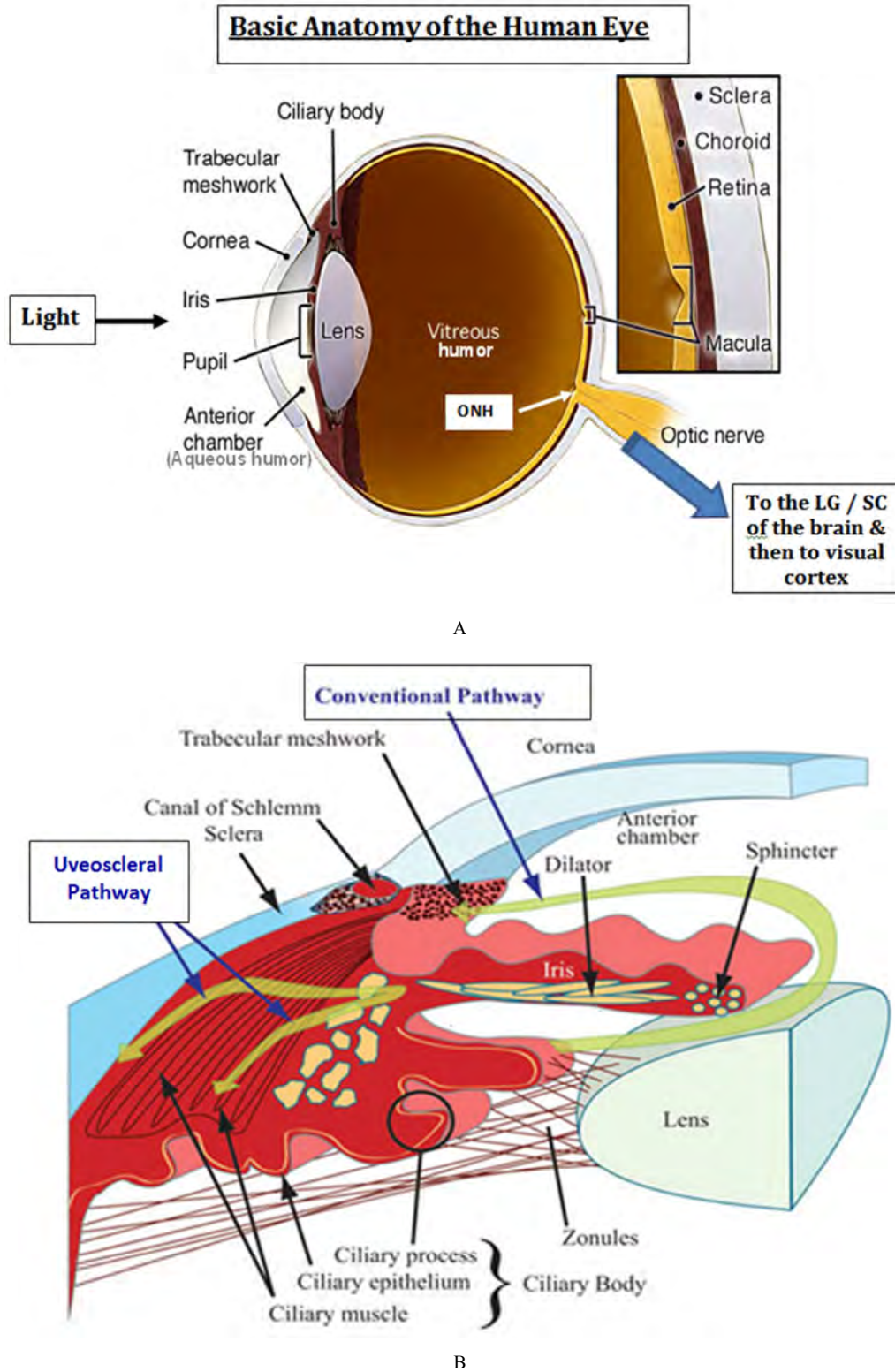
Aqueous humor (AQH) in the anterior segment and vitreous humor (VH) in the posterior segment of the eye, encased in a tough fibrous materials (the sclera), provide the necessary pressure to help maintain the shape of the human eye globe (Fig. 1A). Level of AQH is maintained by an equal rate of AQH production (2 $\mu$ l/hour by the ciliary body) and the rate of its efflux through the trabecular meshwork (TM) via the canal of Schlemm located at the corner of the iris-corneal junction [1] (see Figs. 1A/1B below).

As in the rest of the body, hypertension within the eye is caused by increased resistance, but in this case due to accumulation of cellular debris and various components of extracellular matrix (ECM) in the TM and Schlemm’s canal (SC) drainage system [2-5]. The latter dysfunction is age-

related but some patients are more predisposed to this than others [6, 7]. Indeed, such ocular hypertension (OHT), due to elevated intraocular pressure (IOP), is one of the major risk factors associated with the optic neuropathies known as “glaucoma” [2-7]. Whilst many forms of glaucoma exist [10-12], primary open-angle glaucoma (POAG) has the highest prevalence globally, and it causes irreversible blindness if left untreated [3-5]. In fact POAG ranks as the second leading cause of preventable blindness (after cataracts) afflicting millions of people, with projections ranging from ~80 million by 2020 to >112 million by 2040 [13, 14]. Associated with such global visual impairment is poor quality of life, lost revenue and a huge medicinal and/or surgical treatment burden on nations around the world [3-5; 13, 14]. As the search for genetic markers [15] and potential cures [16-18] for POAG and the related OHT continues, a number of

pharmacological agents [19-23], surgical procedures [24-26] and devices [27-31] have become available to at least treat the symptoms of POAG, vis-à-vis mitigation of OHT. Before

tackling the treatment modalities it is important to understand how elevated IOP is believed to cause visual impairment leading to blindness.



**Figure 1.** Outline of the basic overall anatomy of the human eye illustrating some of the key features discussed in the text. LG denotes lateral geniculate; ONH denotes optic nerve head; SC denotes superior colliculus (Fig. 1A). In Fig. 1B, the key elements of the AQH synthetic machinery (ciliary epithelium), and AQH outflow via the trabecular meshwork (conventional outflow) and via the uveoscleral pathway from the anterior chamber are shown. Note: none of the elements shown are to scale. Original figures were obtained from various on-line sources and then modified to fit the needs of the current article.

### *Pathophysiology of OHT and POAG Leading to Blindness*

While the prominent and pervasive trigger in POAG is the elevated IOP [2-4], it is the down-stream events and associated factors that actually cause the damage to the visual system that culminates in blindness. The mechanical effects of too high a fluid pressure in the anterior segment of the eye is transmitted throughout globe and heavily impacts the retinal ganglion cells (RGCs), their axons and the optic nerve [32, 33] where it exists the rear of the eye. Elevated IOP is thought to excessively stretch the axons of the most peripheral RGCs (closest to the sclera) and cause them to break leading to the demise of their cell bodies, thereby adding stress to the next layer of axons. As this trauma progresses, the optic nerve begins to thin and to bow like heavy wires on an electric pylon, thereby bending and crimping the surrounding blood vessels [33-38]. Such mechanical stress at the lamina cribosa and ONH triggers local macrophages and/or glial cells to release matrix metalloproteases (MMPs) that begins to digest the ECM thereby thinning and excavating the area where the optic nerve exits the eye [39-43]. The resultant constriction of the ciliary and central arteries and their capillaries causes varying amounts of additional local hypoxia / ischemia and reperfusion [34-38]. This oxidative and neurochemical stress disturbs the metabolic profile of the various retinal cell types and reactive astroglial activation initiate release of various noxious chemicals. The latter includes reactive oxygen species, nitric oxide, glutamate and a variety of inflammatory cytokines (e.g. various interleukins) and chemokines ensues [39-46]. It is believed that retina with its high metabolic rate, begins to deplete its mitochondrial energy sources [47-52], and since RGCs are highly sensitive to hypoxia and to these damaging chemicals [52-57], which also include endothelin [49-54], they are unable to sustain cellular homeostasis. The ensuing ionic over-load leads to swelling and eventual RGC death. As the demise of some of the RGCs progresses they empty the contents of their cytoplasm and this leads to more damage of the RGCs in the immediate vicinity of the dying cells. This process continues unabated, albeit very slowly. The dead RGC axons undergo phagocytosis and pruning by macrophages [52-60], and the thinning of the retinal nerve fiber layer (RNFL) and the optic nerve continues [39-45]. Concomitantly, the fragile area where the RGC axons merge to form the optic-nerve-head (ONH; [lamina cribosa]) also feels the physical pressure and weakened RGC axons break, thereby killing their respective RGC neurons in a retrograde manner. As this process continues, the ONH of the optic nerve and the associated blood vessels bend even more [38, 46, 52] leading to further ischemia and retardation of anterograde and retrograde axonal transport of nutrients and growth factors. The combination of the resultant oxidative stress [47-52], neurotrophin deprivation [52, 61], neurotoxicity [48-50, 54] and local inflammation [43, 44, 48] lead to further demise of the RGCs and their axons. Such axonal atrophy thins the optic nerve causing it to buckle even more, that then kills even more RGCs. The end result of this

vicious cycle is a severe loss of retinal connections to the lateral geniculate and the visual cortex of the brain leading to visual impairment [63-66]. Even though these deleterious processes may take years, since there is no overt pain or other warning signal perceived by the patient, the insidious and progressive damage continues unabated. During early to mid-stages of POAG induced by OHT the first signs perceived by the patient are dark spots in the images of the outside world giving the impression of missing details within the images, loss of depth of perception and decreased contrast sensitivity. This is followed by a loss of overall peripheral vision giving a "tunnel vision" syndrome [3-8, 67-70]. As the damage and disease progress over several more years, vision continues to deteriorate and eventually total blindness results. Sadly, most patients only realize the visual deficits setting in after demise of about 40% of their original 1 million RGCs. Thus, OHT causes a slow but progressive loss of vision that develops over several decades. Due to lack of symptoms and suitable diagnostic tools, many people do not even know they have POAG until significant damage has already occurred in their visual system. Thankfully since other risk factors for POAG (apart from OHT) [3-8], including increasing age, race (especially African and Asian heritage), myopia, genetic factors, diabetes and vascular dysfunctions have become known, at least there is increasing public awareness of their risk for visual impairment. Accordingly, regular visual exams and consultation with ophthalmologists are leading to earlier diagnosis and treatment for POAG and associated OHT.

In recent years, it has also become clear that it is not just elevated IOP that causes the damage to the visual system in glaucoma. Since the retina and optic nerve are connected to the central nervous system (CNS) [68-70], and the optic nerve is bathed in cerebrospinal fluid (CSF) [71, 72] and surrounded by three layers of thin membranes, disturbances within this microenvironment also have grave effects on the health of the optic nerve and its components. Thus, the hydrostatic pressure gradient between the intraocular space (high pressure) and the retrobulbar space (low pressure) adversely affects the fragile lamina cribosa of the ONH causing it to undergo remodeling and breakage. Since a low CSF pressure [71, 72] is mirrored by a low systemic blood pressure, especially at night, this causes a high trans-lamina cribosa pressure differential and abnormal fluctuations ("spikes") in IOP [52, 64] that adversely impact RGCs and the ONH. Therefore, there is now an emerging link between systemic blood pressure and low ocular blood flow [33-39], CSF pressure [71, 72], and IOP [1-5, 20-31]. Vascular dysregulation [33-38] is thus, in part, responsible for the onset and/or progression of glaucomatous optic neuropathy leading to eventual loss of sight.

### *Ocular Hypotensive Therapies*

Elevated IOP is intimately linked to glaucomatous damage [2-5] and thus ophthalmologists have targeted this readily measurable and treatable biomarker [17] in an effort to treat POAG [20-31, 73]. Due to the high correlation of high IOP with RGC death and glaucoma [32, 40, 44, 62-64] a number

of useful tools have been developed to reliably and reproducibly measure IOP in patients and laboratory animals in order to guide and provide appropriate treatment(s) [75]. The ultimate goal is to achieve an IOP < 12-13 mmHg in order to preserve RGC function and maintain good visual acuity even though the “normal range” of IOP is considered to be 12-22 mmHg [2-5, 75]. Very few drugs or devices actually achieve this level of sustained IOP reduction but

every mmHg decrease in IOP reduces the progression of POAG by 13% and is therefore considered beneficial as illustrated by multiple clinical trials [3-5, 76, 77]. Likewise, it's been shown that a 50% reduction in rate of visual field loss can be achieved by lowering of IOP by only 20-40% [3-5, 63, 64]. These desired levels of IOP reduction need to be considered when comparing relative efficacies of drugs and devices, along with their overall therapeutic indices.



**Figure 2.** A pictorial view of the outside world seen through normal eyes without visual impairment, and then the same photo as seen through glaucomatous eyes where the peripheral vision is diminished, thus often resulting in “tunnel vision”. The original figures were obtained from the National Eye Institute (NEI) website online and modified to fit the needs of the current article.

Reduction of AQH production and/or acceleration of AQH drainage from the anterior chamber by pharmaceutical means are primarily used to reduce and control IOP [1-5, 24-31]. However, the inadequacies of these medicines either in terms of overall efficacy, duration of action, local and/or systemic side-effects necessitate the discovery and development of new drugs that lack these problems or where such liabilities are reduced. However, patients who are refractory to pharmacotherapy, or are on multiple drug treatment regimens, often require more invasive procedures such as surgical/laser-induced ablation of some of the TM and SC [25, 26]. Drainage of AQH can also be achieved using shunts, valves and micro-invasive-glaucoma-surgeries (MIGS) [27-31]. IOPs of glaucoma patients are routinely monitored and prescription medicines are applied topically to the cornea to either suppress AQH production using inflow inhibitors [1, 20-23], or to stimulate AQH outflow via the trabecular meshwork (TM) (“conventional outflow”) [73, 78, 79], and/or via the uveoscleral (UVSC) pathway (through spaces between CM fibers and the sclera) [20-23, 73, 78, 79]. The resultant IOP reduction has been demonstrated to diminish RGC death, thereby slowing the development and progression of POAG [3-5; 52; 60; 63-65; 68-70]. Pharmaceutical intervention to lower IOP further in ocular normotensive [76-78, 78-80] patients is still desirable since the trajectory of their visual impairment and declining peripheral visual acuity continues. This is one reason why the normotensive patients may require retinoprotectant regimens on top of ocular hypotensive medications [76, 77]. Various neuroprotective agents have been proposed and consist of anti-oxidants like  $\alpha$ -lipoic acid [81, 82],  $\text{Na}^+$  and  $\text{Ca}^{2+}$ -

channel blocker treatment [47, 83, 84], polyamines [85-87] and N-methyl-D-Aspartate receptor-coupled channel blockers [47-52].

## 2. OHT / POAG Pharmacotherapy Today

One of the earliest pharmacological agents to be used, back in 1875, to treat POAG and associated OHT was the miotic muscarinic agonist pilocarpine [19-23, 88]. However, the inadequate IOP-control by pilocarpine and its side-effects (pupillary constriction and brow-ache) prompted pharmaceutical research that culminated in discovery of carbonic anhydrase inhibitors (CAIs; acetazolamide; dorzolamide; brinzolamide; oral and topical ocular [t. o.]) [20-23, 89]. Whilst CAIs lower IOP they cause conjunctival allergy and hyperemia. The discovery and clinical use of beta-adrenergic antagonists (timolol; betaxolol) [20-23, 90, 91] in the seventies was followed by the introduction of alpha-adrenoceptor agonists (brimonidine; para-aminoclonidine) [20-23] in the nineties that primarily impact ciliary body/processes to cut down generation of AQH (Table 1). Unfortunately, even though beta-blockers are potent and efficacious ocular hypotensives, they cause local burning and stinging and worsening of pulmonary insufficiency, and reduce cardiac contractility and heart rate [20-23]. Likewise, alpha-2 agonists are prone to initiate conjunctival allergies, and cause arrhythmias, elevated blood pressure, headaches, fatigue, hyperemia, dry mouth and even drowsiness [20-23, 92] as they lower IOP. Furthermore and unfortunately,

reducing AQH production is insufficient, and despite twice- or three-times daily instillation of inflow inhibitors, IOP-lowering is achieved only for a few hours and only by a few mmHg. It is also not advisable to reduce the AQH production too much since the nutrients and oxygen within this fluid are essential for the healthy maintenance of corneal endothelial cells, lens and TM cells amongst other structures of the anterior segment.

A revolutionary paradigm shift in POAG/OHT treatment occurred in the 1990s and 2000s when FP-receptor-selective prostaglandin analog agonists (PGAs) (e.g. Latanoprost; Travoprost; Tafluprost) [93] (Table 1) were approved. This represented a novel class of pharmacological agents that promoted AQH outflow through the uveoscleral [UVS] pathway to lower IOP. The PGAs utilized an extracellular-matrix (ECM) remodeling mechanism of action by releasing matrix metalloproteinases (MMPs) that digested the ECM within the ciliary muscle bundles and the scleral tissue [20-23, 93]. Since the PG pro-drugs possess a longer duration of action than the inflow inhibitors, they are only dosed to the eye once daily [20-23; 93-95]. This reduced overall drug and preservative exposure to the ocular surface and ultimately enhanced patient adherence to therapy. Nevertheless, compliance remains a major challenge, and FP PGAs also have side-effects such as causing hyperemia, ocular surface irritation, darkening of the iris and periorbital tissues, lengthening of eyelashes and occasionally causing cystoid macular edema [93-95]. While pilocarpine represents the only approved drug that facilitate AQH outflow through the TM and down the canal of Schlemm (conventional outflow; CNV outflow), recent evidence suggests that FP-PGAs reduce IOP by activating AQH egress from the anterior chamber via both UVSC and CVN outflow pathways since FP receptors are present in both CM and TM [96]. Since enhancing AQH drainage via the TM is the preferred mode of treatment for OHT, another three classes of agents that specifically targets the TM, by relaxing this tissue, include rho kinase inhibitors [97-98], a bifunctional molecule that releases both a PGA and nitric oxide (NO) (latanoprostene bund) [100, 101], and an adenosine A1 receptor agonist [102]. Some of these small molecules have reached late-stage clinical trials and look quite promising. However, the therapeutic index associated with these potential drug candidates remain to be described in more detail prior to approval by health authorities. Additionally, whether they deliver the same or superior efficacy, over a protracted period of time, to the current gold-standards (FP-PGAs) remains to be seen.

Unfortunately, patients whose IOP remains uncontrolled by one medicine, or those who are no longer responsive to a given medication, require adjunctive therapy. This involves beta-blocker or CAI eye-drop instillation during the day, and PGA eye-drops instilled at night. Some patients ultimately require three or more different classes of drugs to lower and control their IOP, and perhaps even surgery as a last resort. Various fixed-dose combination drug products [103, 104] in a single bottle have been approved by some world health

authorities for such ocular hypertensive patients. Some examples of combination formulations include Azarga (brinzolamide 1% + timolol 0.5%), Cosopt (dorzolamide 2% + timolol 0.5%), Combigan (brimonidine 0.2% + timolol (0.5%)), Duotrav (travoprost 0.004% + timolol 0.5%), Simbrinza (brinzolamide 1% + brimonidine 0.2%) and tafluprost + timolol combination [103, 104]. A triple fixed-dose combination formulation consisting of dorzolamide + brimonidine + timolol has recently been shown to lower IOP to a significant extent beyond the efficacy provided by each of the drugs in the combination product and is approved in Mexico [104]. While other combination products are on the horizon, such a triple fixed-dose combination product has yet to be approved by any ministry of health where dual combinations are approved ( $\beta$ -blocker + CAI; CAI +  $\alpha$ 2-agonist;  $\beta$ -blocker +  $\alpha$ 2-agonist; PGA +  $\beta$ -blocker; etc.). Another novel approach has been to generate multifunctional molecules that possess dual activity by virtue of conjugation of a PGA with other IOP-lowering agents [105]. Whilst there is much hope pinned to these novel approaches, an older drug nipradalol that has intrinsic beta-blocker and NO-releasing properties has not gained much prominence in clinical practice [20-23;73]. This may be due to its rather low IOP-lowering efficacy.

The clinical management of IOP associated with POAG and OHT has clearly advanced in recent years. However, due to the side-effect profiles of many of the approved pharmaceutical agents described above, there still remains a need to find even better medications for OHT treatment. Some of the ocular and/or systemic side-effects that limit the utility of the current topical ocularly utilized medicines involve their overall effectiveness, duration of action, posology and/or significant side-effects (local irritation/stinging/redness and/or bradycardia and exacerbation of asthma). The duration of action is a key hurdle for some of the afore-mentioned non-PG drugs, since they only provide efficacy for  $\leq 12$  hours. Thus, CAIs (e.g. dorzolamide and brinzolamide) have to penetrate cornea/conjunctiva/ciliary epithelial cell membranes and then block almost 100% of the CA-enzyme activity within the NPE cells to reduce AQH generation. Additional hurdles include the prevalence of several isoforms of the CA with each having a different replenishing rate as the enzymes are synthesized from scratch. These aspects necessitate twice/thrice daily instillation regimen to achieve sufficient IOP reduction and control, and the burden of attendant local ocular irritation and redness (hyperemia). Sharp stinging and burning of the ocular surface is associated with topical ocular  $\beta$ -blockers such as betaxolol and timolol. Additionally, such  $\beta$ -adrenoceptor antagonists reach the systemic circulation from the ocular-nasal duct and produce pulmonary and cardiac side-effects that then limit their utility in asthmatic and hypertensive patients. While FP-receptor PG agonists (PGAs) potently and efficaciously reduce and control IOP for up to 24 hrs and represent first-line ocular hypotensives, they are responsible for local hyperemia, thickening and elongation of eye-lashes, and darkening of the iris and

periorbital area, plus cystoid macular edema in some cases. Even though the latter side-effects are apparently reversible upon PGA drug discontinuation, the long-term consequences of the latter side-effects remain unknown and due caution is

still required in the use of these agents. Therefore, the search for better tolerated and more effective ocular hypotensive drugs continues around the globe. These are discussed more fully in the section below.

**Table 1.** Selected IOP-lowering agents and their reported or potential mechanisms of actions.

Compound classes	Investigative agent or approved drug	Reported or potential mechanism(s) of action
<b>Conventional Outflow (via TM pathway) Promotors</b>		
Muscarinic receptor Agonists	Pilocarpine [88]; Aceclidine; Carbachol	Contract ciliary muscle /TM to promote outflow of AQH via the TM-SC pathway
Inhibitors of chloride transport	Ticrynafen, Ethacrynic acid; Indacrinone [172]	Inhibition of Na <sup>+</sup> -K <sup>+</sup> -Cl <sup>-</sup> -transporter activity in the TM changes cell shape & volume and thus AQH efflux is increased
Kinase inhibitors	ROCK inhibitors [97-99]: Y-27632; Y-39983; H-7; ML-9; Chelerythrine; Staurosporin; K-115; AR-12286; LIM-K inhibitor [165], Myosin-II ATPase inhibitor: Blebbistatin Sc kinase inhibitor [166]	Modification of actomyosin contractility that leads to changes in actin cytoskeleton of TM and this leads to AQH efflux; direct relaxation of the TM may also be involved.
Marine macrolids	Latrunculins A and B; Bumetanide; Swinholide [79]	Promote sequestration of actin monomers and dimers in TM; cause cell TM shape change and thus AH efflux
Guanylate cyclase activators NO Donors Soluble guanylate cyclase activators	Natriuretic peptides: ANP; CNP [167] sodium nitroprusside; Hydralazine; 3-morpholinolinosyndnonimine; (S)-nitrosoacetylpenicillamine; NCX-125 [100, 101] IWP-953 [119]	Type-A and type-B receptor activation leads to cGMP production, TM relaxation and AQH efflux via TM
κ-opioid receptor agonists	Bremazocine; dynorphin [168]	Release natriuretic peptides and thus raise cGMP in TM leading to its relaxation & thus AQH efflux
Cannabinoid receptor agonists	WIN55212-2; CP55940; SR141716A [169]	Receptor stimulation opens BKC-channels and relaxes TM which then causes AQH efflux via TM and SC.
FP-class PG-receptor agonists	Latanoprost; Travoprost; Bimatoprost; Tafluprost; Unoprostone isopropyl ester [93-96; 170]	Some clinical evidence of promoting conventional outflow in addition to UVS outflow
Serotonin-2 receptor antagonists	BVT-28949; ketanserin and its analogs [171]	Unknown and unverifiable mechanism(s) of action (may block beta-adrenergic receptors indirectly?)
Releasers of MMP & AP-1	FP-class PGs [93-96]; <i>t</i> -butylhydroquinone ( <i>t</i> -BHQ); β-naphthoflavone;	Local production of MMPs; ECM degradation; stimulation of AQH efflux via TM
<b>Uveoscleral Outflow promotors (via CM bundles and sclera)</b>		
FP-class PG-receptor agonists	Latanoprost; Travoprost; Bimatoprost; Tafluprost; Unoprostone isopropyl ester [93-96;170]	FP receptor activation in CM causes release of MMPs that breakdown ECM (“clog”) around CM bundles and within sclera thus causing UVS outflow of AQH
EP <sub>2</sub> - and EP <sub>4</sub> - PG-receptor agonists	AL-6598 [93, 121]; Butaprost; ONO-AE1-259-01; PF-04217329 [122]; DE-117 (Omidenedap Isopropyl) [110, 123]; PF-04475270 [120]	Receptor activation increases cAMP that relaxes CM & TM; EP <sub>2</sub> agonists also cause release of MMPs that breakdown ECM (“clog”) around CM bundles and within sclera thus causing UVS outflow of AQH
Serotonin-2 (5HT-2) receptor agonists	(R)-DOI; α-methyl-5HT; AL-34662 [124-126]	Contraction / relaxation of CM and TM by activation of 5HT <sub>2</sub> receptors. May also release MMPs and/or PGs or other local mediators that promote CM remodeling and thus promote UVS outflow
Bradykinin B <sub>2</sub> -receptor agonists	Bradykinin; FR-190997; BKA278 [135-146]	B <sub>2</sub> -receptor activation causes PI hydrolysis production of IPs and DAG; cause PG release and release of MMPs that digest ECM and this promote UVS outflow in cynomolgus monkey; conventional outflow also stimulated in isolated bovine /porcine anterior eye segments [177, 178].
Dual pharmacophore PGs	FP/EP <sub>3</sub> receptor agonist (ONO-954) [127, 128]	Promote UVSC outflow and TM outflow
<b>Inflow inhibitors (reduce AQH production)</b>		
β-adrenergic antagonists	Betaxolol; Levobetaxolol; Timolol; Levobunolol; Metipranolol [19-23]	Block β-adrenergic receptors in the ciliary process, decrease cAMP generation and thus decrease AQH formation
α <sub>2</sub> -adrenergic agonists	Brimonidine; Clonidine; Apraclonidine [19-23]	Intracellular cAMP reduced in CP that decreases AQH generation; may also prevent NE release. Brimonidine also promotes TM outflow
Carbonic anhydrase inhibitors	Dorzolamide; Brinzolamide [89]	Inhibit ciliary process CA-II and CA-IV and thus reduce bicarbonate production that in turn reduces AQH generation
Chloride channels inhibitors	5-nitro-2-(3-phenylpropylamino)-benzoate [172]	Ion flux of CP NPE cells causes reduction of AQH formation
Na <sup>+</sup> -K <sup>+</sup> -ATPase inhibitors	Ouabain; Digoxin analogs [173]	Ciliary process Na <sup>+</sup> -K <sup>+</sup> -ATPase inhibited leading to inhibition of AQH production

Compound classes	Investigative agent or approved drug	Reported or potential mechanism(s) of action
Dopamine receptor agonists	PD128907; CHF1035; CHF1024; SDZ GLC-756; (S)-(-)-3-hydroxyphenyl-N-n-propylpiperidine (3-PPP) [174]	Inhibit release of NE & prevent AQH production; may also release natriuretic peptides
Na <sup>+</sup> -K <sup>+</sup> -ATPase inhibitors	Ouabain; Digoxin analogs [173]	Ciliary process Na <sup>+</sup> -K <sup>+</sup> -ATPase inhibited leading to inhibition of AQH production
Aquaporin Inhibitors	Various aromatic sulfonamides and dihydrobenzofurans [180]	Inhibit release of NE & prevent AQH production
<b>Other IOP-lowering agents</b>		
Mas receptor stimulator	DIZE via ACE-2 activation [131]	Prevent ECM (including TGFβ) accumulation (outflow stimulation ?)
Angiotensin-II receptor antagonists	CS-088 [129]	Various mechanisms of action; not robust IOP-lowering
Ca <sup>2+</sup> -channel inhibitors	Lomerazine; Nivaldipine; Nifedipine; Nimodipine; Verapamil; Brovincamine; Iganidipine [84]	Enhance retinal blood flow; some may lower IOP; work well in normal tension glaucoma patients
Alpha-adrenergic receptor antagonists	Oxymetazoline; 5-methylurapidil; Ketanserin [175]	Work mostly via outflow mechanism but this needs to be defined
Other prostaglandin receptor agonists	AL-6598 (DP/EP <sub>2</sub> receptor agonist); AGN192093 (TP receptor agonist); BW245C (DP receptor agonist); Sulprostone (EP <sub>3</sub> receptor agonist) [19-23; 121]	These work through multiple mechanisms of action involving cAMP production, Ca <sup>2+</sup> mobilization leading to relaxation / contraction of ciliary muscles/ TM
PG-conjugates [101, 105]	Latanoprostene Bunod (NO donor coupled to latanoprost) [101]	Combination of NO-cGMP production and FP-receptor activation
Combination products	Brinzolamide-brimonidine; Brinzolamide-brimonidine; Acetazolamide-Timolol-Brimonidine; Travoprost-brimonidine; Bimatoprost-brimonidine; Tafluprost-Timolol [103, 104]	Complementary mechanisms of action encompassing inflow-outflow inhibition, and inflow-uveoscleral outflow inhibition.

#### *POAG / OHT Pharmacotherapy: Tomorrow and Beyond*

The continued and concerted efforts of researchers in academia and industry is providing new targets and pathways for pursuit of new ocular hypotensive drugs and agents that could potentially protect the RGCs in a more direct manner. Development of more robust and translatable animal models of OHT/glaucoma involving numerous animal species [10-12, 23, 88, 93, 106-110], ex-vivo ocular models (e.g. perfused anterior eye segments [107]), and new screening assays and techniques [20, 40, 42, 46, 47, 62, 65, 74, 75], including biomarkers [17] are helping advance our knowledge of the etiologies of OHT and POAG. Similarly, development and use of methods to detect RGC death in real-time [111], ocular metabolomics [112], ocular proteomics [113], radiowave telemetric recording of IOP [114] and refined computer modelling of visual field progression [115] is proving of immense value in the diagnosis and prognosis of OHT and POAG. This in turn is helping discover new ways and novel agents to treat these diseases. Pharmacological agents that have shown promise in combating OHT in various assays and animal models include NO- and hydrogen sulfide- donors [116-118], soluble guanylate cyclase activators [119], rho-kinase inhibitors (e.g. Y-39983, K-115, AR-12286, AR-13324, and AMA0076) [79, 97-99], PG-NO donor conjugates (e.g. Latanoprostene bunod [BOL-303259-X]) [101], adenosine receptor agonists (e.g. OPA-6566; CF-101; Trabodenosone) [102], EP<sub>4</sub> PG-agonists (e.g. 7-dithia PGE1; PF-04475270) [120], EP<sub>2</sub> receptor PG-agonists (e.g. AL-6598; ONO-AE1-259-01; PF-04217329; DE-117 (Omidenepag Isopropyl™) [93, 121; 122-124], serotonin-2 (5-hydroxy-tryptamine-2 [5-HT<sub>2</sub>]) receptor agonists (e.g. R-DOI; AL-34662) [125, 126], dual pharmacophoric PGs, having both FP- and EP<sub>3</sub>-receptor agonist activities (e.g. ONO-9054) [127, 128], dopamine

receptor agonists, melatonin receptor agonists, cannabinoid agonists, receptor-coupled-guanylate cyclase activators, etc (Table 1).

An area of research that overlaps between the systemic hypertension and OHT relates to the renin-angiotensin and kallikrein-kinin systems. Local intrinsic location and production of various components and products of the renin-angiotensin system (RAS) that activate distinct receptor-effector pathways have now been delineated in anterior uveal ocular cells and tissues. Furthermore, angiotensin converting enzyme (ACE) inhibitors, angiotensin (AT) receptor antagonists [129], a novel angiotensin-derived peptide (Ang-1-7) [130] and a novel ACE-2-activator [131] have demonstrated ocular hypotensive [129-132] and neuroprotective [131] activity in various animal models [129-133]. However, at present less is known about translation of these findings to the human OHT patient population, but warrants further investigation.

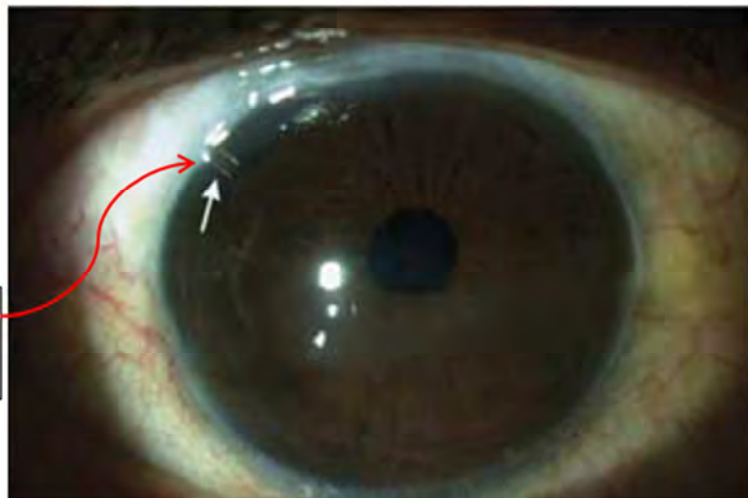
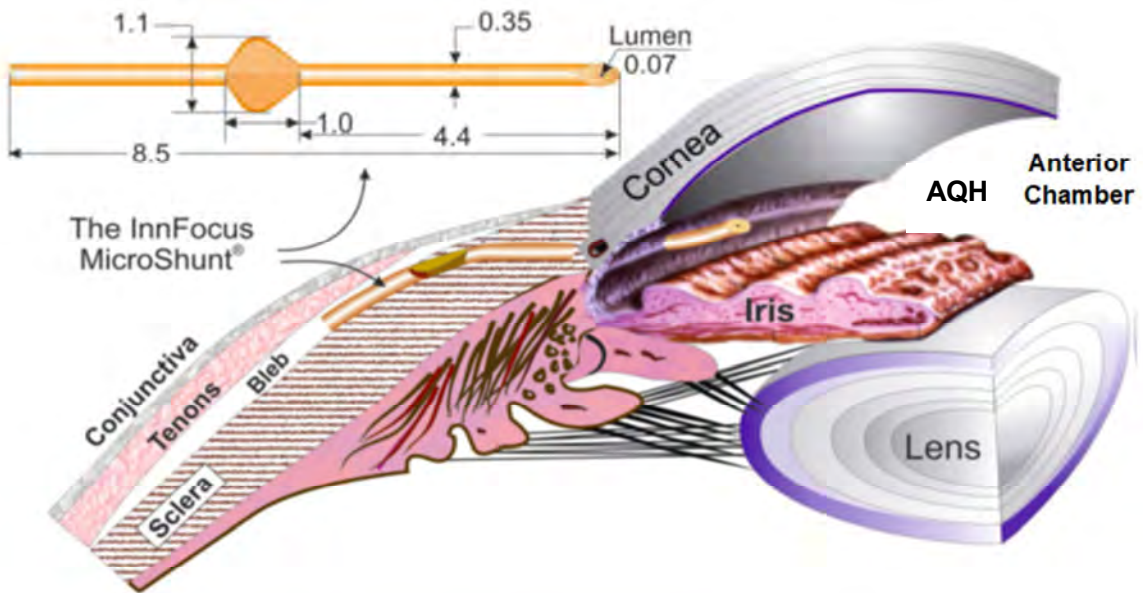
Recent research has provided strong evidence for an endogenous local enzymatic system that generates various kinins in cells of tissues involved in IOP regulation [134-138]. Indeed, bradykinin (BK) and various BK-related peptides (and some BK-mimetic non-peptidic agents FR-190997; BK2A78) [139, 140] stimulate B<sub>2</sub>-receptors in animal and human cells derived from ciliary body (both epithelial and smooth muscle) [141, 142] and TM [138, 144] to generate intracellular inositol phosphates, intracellular Ca<sup>2+</sup> and promote secretion of PGs and MMPs [141-146]. Such cellular and molecular cascades are now believed to be responsible for causing profound lowering and controlling IOP with a long duration of action in ocular OHT cynomolgus monkey eyes [145, 146]. Again, whilst translation of these observations in OHT patients is eagerly awaited, the afore-mentioned lead compounds (FR-190997;

BK2A78 [145, 146]) represent new drug candidates and potential novel templates for further studies in this arena.

### 3. Microinvasive Glaucoma Surgeries (MIGS) and Devices

As mentioned earlier, it is the elevated IOP due to AQH accumulation in the anterior chamber of the eye that causes glaucomatous damage to the optic nerve. Obviously if the AQH can be drained in a controlled manner, and on a slow continuous basis, an homeostatic state would be achieved thereby normalizing IOP and preventing RGC death. To this end, laser-induced TM ablation and surgical procedures [24-26] have been enhanced by implantation of tiny devices (microshunts) [27-31] into the anterior chamber of the eye. The classic laser-treatment and surgery that pertains to removal of some of the TM tissue is quite an effective procedure because endogenous ocular hypotensive agents are

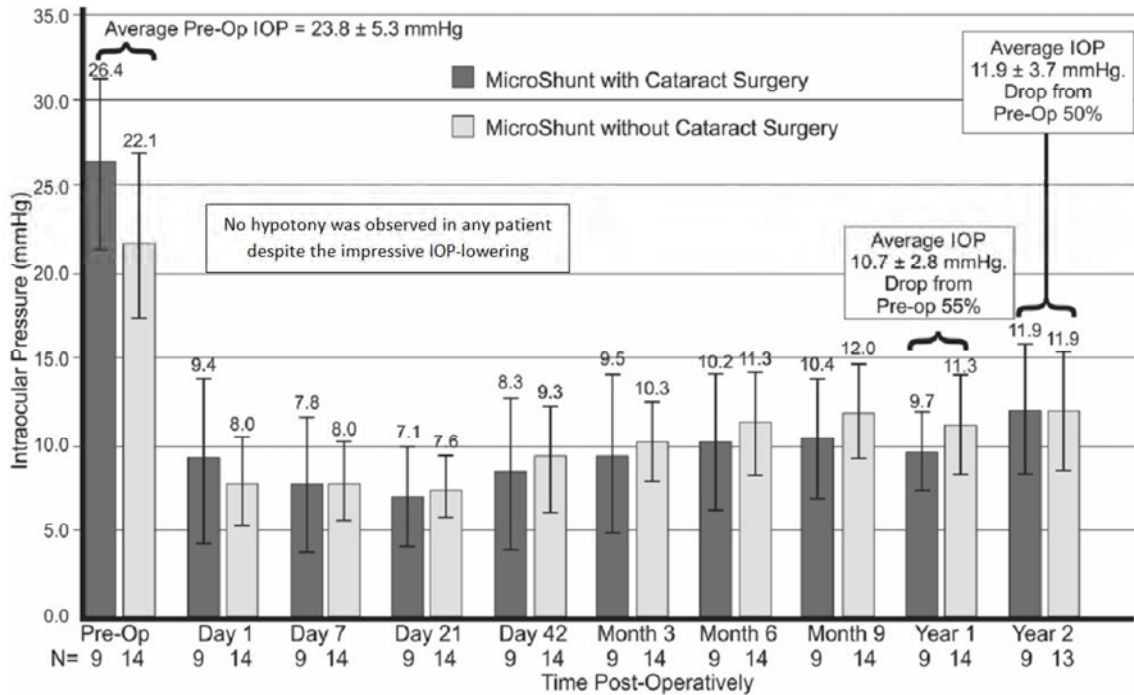
released into the AQH that promote AQH efflux from the anterior chamber [24-26]. However, the latter procedures are confounded by the rather short duration of IOP-lowering efficacy and robust ocular healing process that seals the opening and scars the sclera, thereby necessitating further lasering and surgery. Consequently, it was believed that once an orifice is created from the anterior chamber for AQH egress, that implantation of a device that remains in the anterior chamber and extrudes the AQH fluid out to the sclera, conjunctiva and sub-tenons space would be more effective than the surgery alone. Indeed several devices have been tested in animals and humans and one recently approved by the FDA, iStent [27-31]. Another very efficient device is the InnFocus MicroShunt™ that lowers the IOP in POAG/OHT patients down to 10-12 mmHg and maintains the IOP close at to this level for up to 3-years [29] (see Figs. 3-4 below).



MicroShunt is so small, it's barely visible

**Figure 3.** Top portion of the figure depicts an InnFocus Microshunt™ (IFMS; dimensions and its positioning inside the front of the eye to drain the AQH from the anterior chamber to the sub-tenons space). The lower portion of the Figure shows the location of an implanted IFMS in a human eye (front view). Modified from ref 29.





**Figure 4.** This figure depicts the lowering and controlling of IOP in numerous patients who had the InnFocus Microshunt™ (IFMS) implanted into their eyes in absence or in conjunction with cataract surgery. The IOPs were monitored and recorded over many months and years as shown to demonstrate the longevity of the ocular hypotension induced by this device. No hypotony was observed. Modified from ref 29.

Due to the extraordinary ocular hypotensive effect and the maintenance of low IOPs for years (Fig. 4), such micro-devices are going to revolutionize the treatment for ocular OHT, POAG and other forms of glaucoma. These MIGS-coupled devices have the potential for replacing some of the topical ocularly applied medications. This is indeed an exciting time for ophthalmology and the patients afflicted with OHT and glaucoma. Preservation of vision by any safe and effective means continues to be a goal for all ophthalmologists and researchers involved in cutting-edge research. We should be encouraged by these new findings and hope for more rapid progress in this arena of tackling the undesirable effects of old age and other ocular pathologies connected with POAG and OHT.

#### OHT and Neuroprotection

Since some patients continue to lose vision despite having their IOP under control, such as in ocular normotensive glaucoma [33, 39, 76, 77], there is a need to reduce or prevent the apoptotic death of RGCs. Consequently, direct protection of RGCs, independent of lowering IOP, has become an important avenue of glaucoma/OHT research. However, despite many drug candidates having demonstrated efficacy in isolated cells and in animal models of RGC demise, none have proven effective in human clinical trials thus far. Agents that have been investigated and shown positive results in animal studies include anti-oxidants (e.g.  $\alpha$ -lipoic acid) [81, 82] glutamate / N-methyl-D-Aspartate receptor-channel antagonists (e.g. MK-801; memantine) [47, 50, 52, 55, 60, 147], caspase and NOS inhibitors [52, 55, 60, 67, 148], neurotrophic factors (e.g. nerve growth factor; brain-derived growth factor) [149-151], alpha-2 agonists (e.g.

brimonidine) [150, 152, 153], beta-blockers (e.g. betaxolol) [149, 154, 155], delta opioid agonists [156], etc. Continued research effort in this area to mitigate glaucomatous optic neuropathy would eventually be rewarded. Drugs that directly protect the RGCs and their axons and thereby preserve vision are thus eagerly awaited.

## 4. Conclusions

In conclusion, hypertension of the eye is intimately involved in causing serious and blinding visual impairment around the world. It is believed that physical and mechanical effects of the elevated IOP leads to apoptotic death of RGCs which in turn leads to loss of their axonal connections to the brain thereby negatively impacting vision. Since every mmHg of IOP reduction is important, many pharmaceutical small molecule drugs have become mainstay treatment modalities for combating OHT, with FP-class PGAs being the most preferred due to their extraordinary efficacy. Hopefully the new non-PG EP<sub>2</sub>-receptor agonists such as omidenepag isopropyl (DE-117), and ROCK inhibitors such as Netarsudil [97] will continue to demonstrate long duration of IOP-lowering efficacy with reduced or minimal side-effects. Combination products have also been introduced into clinical management of OHT since some patients are refractory to certain medications and/or whose IOP is not controlled by one drug. Furthermore, fixed-dose ocular hypotensive combination products have alleviated some of the compliance issues associated with topical ocular drugs. In recent years implanted valves/shunts and MIGs to promote efflux of AQH from the anterior chamber have also become

important tools to overcome the destructive effects of elevated IOP. It is hoped that steady progress in the discovery, development and regulatory approvals of novel medications and devices will continue in order to help preserve vision of POAG patients. Clearly, advances in ocular genetics and metabolomics-wide association studies [157], a better understanding of AQH dynamics and lymphatics [158-160], refinement of clinical trials, both for OHT [161] and neuroprotection [55, 147], will also be very useful. Likewise, use of novel molecules such as vitamin B3 [18], micro-RNAs [162] and transplantation of stem cell [163, 164] could also prove of value in the fight against OHT/glaucoma, including glaucomatous optic neuropathy (GON).

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