Chapter 7
Ocular Hypotensives and Neuroprotectants in Glaucoma

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Abstract Glaucoma is the leading cause of blindness in the world. It is an optic neuropathy disease associated with elevated intraocular pressure. Glaucoma encompass a group of various clinical presentations that share the same anatomical feature, a progressive loss of retinal ganglion cells (RGCs) superior to the age-related loss. This chapter deals about the pharmacology of conventional antiglaucoma drugs and newer drugs/pathways which are under investigation. Medical management of glaucoma has been discussed with the concept of reaching target intraocular pressure ("Target IOP") using pharmacological agents. Newer concept of neuroprotectants for the management of glaucoma has also been included in the deliberations.

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7.1 Pharmacological agents in the medical management of glaucoma

7.1.1 Background

The glaucomas encompass a group of various clinical presentations that share the same anatomical feature, a progressive loss of retinal ganglion cells (RGCs) superior to the age-related loss. Glaucoma is still the first cause of irreversible blindness worldwide, and it has been estimated recently that the number of glaucoma cases will be 76 million in 2020 and about 112 million in 2040. Glaucoma is the second leading cause of blindness in the world. Primary open-angle glaucoma (POAG) is the most predominant form of glaucoma worldwide, accounting for 74 % of those affected (Kingman 2004). POAG is characterized by progressive retinal ganglion cell loss, optic nerve damage, and visual field loss leading to bilateral blindness in about 10 % of untreated individuals. Aqueous humor is a clear fluid which is secreted by the ciliary epithelium in the posterior chamber and travels to the anterior chamber wherein it nourishes the avascular tissues like the cornea and lens and drains into the episcleral vein through the trabecular meshwork (TM) (Fig. 7.1). Pharmacological management of glaucoma is achieved by either decreasing the aqueous production or by facilitating the aqueous outflow. Drugs with their target, mechanism of action in reducing IOP are shown in the Table 7.1. The goal of treatment of all patients with glaucoma and those suspected of having glaucoma is the same, specifically enhancing their quality of life, helping them celebrate life, and allowing them to be as healthy as they can.

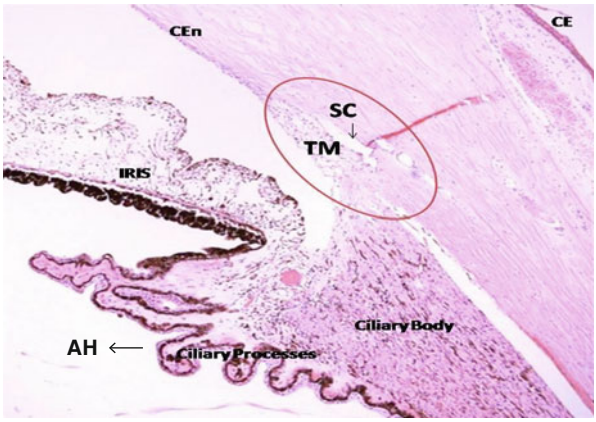


Fig. 7.1 Aqueous humor (AH) outflow pathway (*abbreviation*: *CE* corneal epithelium, *CEn* corneal endothelium, *SC* Schlemm's canal, *TM* trabecular meshwork)

Table 7.1 Classification of drugs, their target, and expected pharmacological effect used for the treatment of glaucoma

	Classification	Target	Pharmacological effect	Drugs
1.	*Beta-blockers*			
		β-1, β-2 blocker	Reduces aqueous humor (AH) production	Timolol, levobunolol, carteolol, and metoprolol
		β-1 selective blocker	Reduces AH production	Betaxolol
2.	*Alpha agonists*			
		α-1 receptor	Vasoconstriction-induced reduction in AH or enhanced outflow	Epinephrine and dipivefrin
		α-2 receptor (pre- and postsynaptic stimulation)	Decrease in sympathetic outflow and stimulation of Gi-mediated reduction of cAMP → decreased AH	Apraclonidine, brimonidine
3.	*Parasympathomimetics*			
		M_3 receptors	Facilitates aqueous outflow by producing traction on scleral spur or trabecular meshwork	Pilocarpine and carbachol
		Inhibition of cholinesterase	Indirectly facilitates stimulation of M_3	Echothiophate and physostigmine
4.	*Prostaglandin analogs*			
		Prostanoid FP receptor	Facilitates uveoscleral outflow	Latanoprost, bimatoprost, travoprost, tafluprost, and unoprostone
5.	*Carbonic anhydrase inhibitors*			
	Systemic	Carbonic anhydrase isoenzymes (II, IV, and XII) inhibition	Reduces the fluid transport by inhibiting bicarbonate ions	Acetazolamide, methazolamide, and dichlorphenamide
	Topical	Inhibition of carbonic anhydrase (higher affinity for type II)	Reduces the fluid transport by inhibiting bicarbonate ions	Dorzolamide and brinzolamide
6.	*Osmotic agents*			
		Plasma osmotic pressure	Increased osmotic pressure in plasma leading to shifting of water from eye → decreased IOP	Mannitol, glycerol

7.1.2 Concept of "Target IOP"

The concept of target intraocular pressure (IOP) arises from the fact that progression in advanced glaucoma, and occasionally in early glaucoma, may occur even at what is thought to be a "normal" intraocular pressure. The erstwhile magic figure of 21 mmHg or lower may not be low enough for many glaucomatous eyes to halt the progressive field damage.

Target IOP is defined as "*a range of acceptable IOP levels within which the progression of glaucomatous neuropathy will be halted /retarded.*" It is the specific level of pressure that, if achieved, will possibly prevent further optic nerve damage and is the IOP where the rate of loss of ganglion cell will equal the age-induced loss (Heijl et al. 2002; Feiner and Piltz-Seymour 2003; Hodapp et al. 1993; Jampel 1997). Further, this concept acknowledges that there may be pressure-independent factors, including aging, which may be superimposed upon the pressure-related process of glaucoma progression. This definition does not suggest that lowering IOP will completely halt progression of glaucomatous disease.

It can also be defined as the IOP at which the sum of the health-related quality of life (HRQ_oL) from preserved vision and the HRQ_oL from not having side effects from treatment is maximized.

7.1.3 Factors Influencing Target IOP

The target IOP is dependent on (Lichter et al. 2001):

(a) IOP level before treatment (the lower the untreated IOP levels, the lower the target IOP should be)
(b) Stage of glaucoma (the greater the preexisting glaucoma damage, the lower the target IOP should be)
(c) Rate of progression during follow-up
(d) Age and life expectancy (younger age requires lower target IOP)
(e) Presence of other risk factors, e.g., exfoliation syndrome
(f) Family history
(g) Systemic diseases (diabetes, HT, CAD, CVD)

The initial target pressure is an estimate toward the ultimate goal of protecting the optic nerve. The target pressure is different among patients, and even in the same patient it may require recalculation in the course of the disease.

When initiating therapy, it is assumed that the measured pretreatment pressure range resulted in optic nerve damage; so, the initial target pressure selected is at least 20 % lower than the pretreatment IOP

7.1.4 Setting Up Specific Target

The specific target IOP can be set by classifying the disease based on the severity of glaucomatous damage as follows:

Mild Glaucomatous optic nerve abnormalities with normal visual fields

- For 20 % IOP reduction from baseline values, keep IOP <18 mmHg.

Moderate Visual field abnormalities in one hemifield but not within 5° of fixation

- For 30 % IOP reduction, set IOP below 15 mmHg.

Severe Visual field abnormalities in either hemifield or field loss within 5° of fixation

- For 50 % IOP reduction, set IOP below 13 mmHg

In addition to setting the target IOP, it is important to keep watch on the *diurnal fluctuation of IOP*. The maximum IOP should always be kept below 18 mmHg at all follow-up visits (AGIS study data), and the fluctuation of IOP (both diurnal and long-term variations) should be below 4 mmHg.

The adequacy of the target IOP needs to be periodically reassessed by comparing optic nerve status (quantitative assessments of the disc and nerve fiber layer and visual field tests) with previous examinations. If progression occurs at the set target pressure, the target IOP should be lowered (Heijl et al. 2002; Feiner and Piltz-Seymour 2003; Hodapp et al. 1993; Jampel 1997; Lichter et al. 2001; AAO Glaucoma 2004–2005). The target IOP is just a guideline; it is better to use a range rather than a single number. Using a range of IOP prevents unnecessary aggressive therapy.

7.1.5 Medical Therapy

The ideal antiglaucoma medication is one that is effective, has minimal side effects, is cost-effective, and is easy to comply with.

Before we proceed further, it's important to understand that a *first-choice agent* is the drug chosen on medical grounds, whereas a *first-line agent* is selected on nonmedical (usually cost) grounds.

There are six classes of topical hypotensive medication: hypotensive lipids (prostaglandin analogues), beta-blockers, selective (alpha 2)-adrenergic agonists, carbonic anhydrase inhibitors (CAIs), cholinergics, and hyperosmotics (Table 7.1). Refer Chapter 6 for the detailed pharmacology of drugs acting through autonomic receptors.

7.1.5.1 Hypotensive Lipids

Hypotensive lipids fall into three subcategories: prostaglandin analogues (PGAs) which include latanoprost (Xalatan 0.005 %) and travoprost (Travatan and Travatan Z, both 0.004 %; Izba which is travoprost 0.003 %), prostamide which includes bimatoprost (Lumigan 0.03 % and 0.01 %), and the deconsanoid class which is represented by unoprostone isopropyl (Rescula 0.15 %). They are all derivatives of prostaglandin F2 alpha, based on pioneering work by Bito, Stjernschantz, and Camras (Bito 2001; Camras et al. 1989).

PGAs increase both trabecular meshwork and uveoscleral outflow (Lim et al. 2008) and are less affected by circadian variations in aqueous production than the beta-blockers (Walters et al. 2004). Although these drugs have dual mechanism of action, most of the increased outflow facility can be attributed to their effects on the pressure-independent uveoscleral outflow pathway.

Variations in the PGF2 alpha molecule result in changes in potency and side effects. Latanoprost was the first one to be developed commercially (by Pharmacia, now Pfizer). In order to reduce the hyperemia associated with PGF2 alpha, the unsaturated (double) bond between carbons 13 and 14 was saturated. This resulted in some loss of potency, but by reducing hyperemia made the drug cosmetically acceptable to patients. Because there is no major clinical difference in IOP-lowering efficacy whether this class of drugs is dosed daytime or nighttime, it has become customary to prescribe them at bedtime, so that the majority of the immediate hyperemia associated with drug dosing occurs while the patient is asleep. These drugs do have some "chronic" hyperemia that tends to subside over several months of use. Occasionally patients prefer morning dosing, which is acceptable from an efficacy perspective. Clinical IOP-lowering efficacy is better with OD dosing rather than BID dosing (Alm and Stjernschantz 1995). Systemic half-life of the drugs is brief (e.g., latanoprost 17 min). There is little effect of the drugs on the IOP of the contralateral eye when dosed unilaterally (Sjoquist and Stjernschantz 2002).

To improve efficacy, Alcon Laboratories modified the PGF2 alpha molecule to create travoprost by adding a CF3 on the unsaturated benzene ring. This allows for a tighter bonding of the travoprost free acid to the FP receptors (Sharif et al. 2003). This results in a longer-duration, clinically useful, IOP-lowering effect of both original travoprost and the BAK-free version, Travatan Z (Gross et al. 2008). This could be important in patients who occasionally miss doses.

Most of the hyperemia associated with the HLs results from dilated conjunctival vessels in response to direct activation of FP receptors found in the vasculature muscle walls. Bimatoprost has a six- to eightfold greater concentration than other hypotensive lipids. This may be related to the clinical observation that bimatoprost causes more red eye than the other two products (Stewart et al. 2003).

The three hypotensive lipids lower IOP on average between 25 and 30 %. These drugs have relatively flat IOP curves over 24 h, demonstrating both low circadian IOP fluctuation and, unlike the beta-blockers, effective diurnal and nocturnal IOP control (Konstas et al. 2005). They do not evidence short-term escape or long-term drift (Goldberg 2001; Cohen et al. 2004; Bayer et al. 2004).

Latanoprost is subject to deterioration when exposed to heat over 100 °F for longer than 8 days (Xalatan package insert, Pfizer, NY). The other hypotensive lipids seem to be somewhat more stable at temperatures likely to be found in most natural settings. All agents may deteriorate at an accelerated pace when exposed to direct sunlight.

7.1.5.2 Beta-Blockers

Topical beta-blockers were considered the gold standard initial treatment for open-angle glaucoma for nearly two decades, from 1978 to 1996, when the first prostaglandin analogue was granted approval by the FDA. Hypotensive lipids (prostaglandin analogues) are more potent IOP-lowering drugs than timolol and other beta-blockers. However, this fact does not mean that beta-blockers cannot be used as a first-line agent. This class of medication still remains efficacious, tolerated, and cost-effective.

Beta-blockers antagonize beta 1 and beta 2 receptors in the ciliary body's nonpigmented epithelium and thereby reduce secretion of the aqueous humor through an incompletely understood mechanism, which in turn lowers IOP. Action on the ciliary microvasculature may reduce the ultrafiltration component of aqueous secretion.

One drop of timolol maleate 0.25 or 0.50 % has its peak effect, 2 h following administration, and may last for 24 h. Some residual effect of timolol on IOP may be detected for as long as 2–3 weeks, and beta blockade can be detected up to 1 month after discontinuation of the drug.

Nonselective beta-blockers lower IOP 20–30 %. However, IOP reduction may be as high as 50 % and last greater than 24 h in some individuals. In up to 20 % of cases, the initial IOP reduction can be lost within 2–3 weeks. This has been called *short-term escape* and most likely reflects an upregulation in the number of ocular beta receptors after initial complete blockade (Boger 1983). For this reason, it is recommended to wait at least 4 weeks following initiation of therapy before assessing IOP effect.

Beta-blocker treatment can maintain control of IOP for years. However, in some patients IOP control may be lost after many years of therapy or even within 3 months (Gieser et al. 1996). This phenomenon is called *long-term drift* and may be the result of drug tolerance or progression of the trabecular meshwork outflow problems.

Selective beta 1 blockers are less potent at reducing IOP than their nonselective counterparts, which can make them less attractive in patients who need a bigger IOP reduction.

The advantage of selective beta 1 blockers is that they have less effect on the beta 2 receptors found predominantly in the pulmonary system, making them more tolerable in patients with the potential for bronchospasm. Among nonselective beta-blockers, there are no differences in terms of IOP-lowering efficacy.

Patients under treatment with systemic beta-blockers may experience a reduced effect of topical administration and increased side effects (Allingham et al. 2005).

There are ocular, cardiovascular, pulmonary, metabolic, and central nervous system side effects. In general, beta-blockers are well tolerated when applied topically; however, there are reports of ocular discomfort due to burning, hyperemia,

toxic keratopathy, punctate keratopathy, periocular contact dermatitis, and dry eye (Dunham et al. 1994).

Chronic administration of benzalkonium chloride (BAK) used as preservative in most beta-blocker solutions may play a role in ocular toxicity. The use of preservative-free timolol may help identify preservative as the source of local side effects. Timolol is available as a solution and in a gel-forming preparation. Gel-forming preparations allow longer permanence on the ocular surface for a sustained effect, and the once-daily administration can lead to fewer side effects. Gel-forming solution is also less likely to reach the nasolacrimal duct, lessening the potential for systemic side effects.

Beta-blockers are absorbed via the nasolacrimal system by the nasal and oral mucosa, thus bypassing the first-pass effect in the liver (Sharif et al. 2003). Direct access to the blood stream explains many systemic side effects and contralateral IOP lowering. Systemic side effects must be thoroughly searched for by a careful medical history since patients often overlook their eyedrops as a potential cause of systemic symptoms.

Beta 1 receptor blockade lowers blood pressure and heart rate, which can cause severe bradycardia, especially in patients with advanced age or underlying medical conditions, such as greater than first-degree heart block (a contraindication for the use of beta-blockers). They also cause decrease myocardial contractility, which is a relative contraindication for beta-blockers in patients affected by heart insufficiency. Exercise-induced tachycardia may be blocked in healthy individuals.

Beta-2 receptor blockade may cause severe asthma attacks. Nonselective beta-blockers are contraindicated in asthmatic patients. They also may exacerbate airway disease in a previously controlled asthma patient or trigger airway disease in a previously undetected or asymptomatic patient. Betaxolol, a beta 1-receptor blocker, has been successfully used in patients with pulmonary disease, but it is not entirely free of potential side effects (Fechtner 1999). A trial of once-daily dosing at the lowest available concentration of an agent (preferably in one eye) would be a good way to start. Only then, if indicated, should the frequency and concentration be increased.

Beta-blockers have been observed to alter the blood lipid profile negatively and could increase the risk of coronary heart disease. They may also mask the symptoms of hypoglycemia, such as tachycardia, in diabetics.

Central nervous system side effects are often subjective in nature and rarely attributed to eyedrops by patients. It is prudent to directly question patients about symptoms of fatigue, lethargy, confusion, memory loss, sleep disturbance, and dizziness. If present, a lower dosage of beta-blocker or replacement with another class of drug should be discussed.

7.1.5.3 Alpha Agonists

The selective alpha-agonist agents used to treat glaucoma are modifications of the clonidine molecule (similar to the development of the hypotensive lipids that were derived from PGF2 alpha).

Two topical alpha-adrenergic agonists are available for glaucoma therapy, apraclonidine which is relatively nonselective for alpha 1 and alpha 2 receptors and brimonidine (Alphagan and generic) that is more selective for alpha 2 than alpha 1 receptors. These drugs work by preventing the release of norepinephrine at presynaptic terminals. They both decrease aqueous production, and they may have some effect on episcleral venous pressure as well as uveoscleral outflow (Reitsamer et al. 2006; Toris et al. 1999). Brimonidine may also affect conventional outflow in a positive manner. These drugs lower IOP between 20 and 25 %.

Apraclonidine (a) does not lower IOP in about 1/3 of patients, (b) has extreme tachyphylaxis (loss of effect) within about 90 days in about 1/3 of patients, and finally (c) causes blepharoconjunctivitis with red eyes, conjunctival follicles, pruritus, and periorbital dermatitis in about 1/3 of patients. Pupil dilation and lid retraction may also occur in a significant fraction of patients (Yuksel et al. 1992).

The newer lower concentrations of Alphagan-P, which contain the preservative purite instead of BAK, seem to be better tolerated, with a decreased incidence of allergy and almost as good intraocular pressure control as with the higher (0.2 %) concentration of the original drug (Whitson et al. 2006).

The pharmacokinetics of topically administered brimonidine requires that it be dosed three times per day, similar to the topical CAIs.

Brimonidine must be used with caution in neonates, young children, and the frail and elderly. With very young patients, brimonidine has resulted in apnea and coma (Mungan et al. 2003). Brimonidine can cause fatigue in elderly. Patients should specifically be queried about the presence of this important side effect. In these groups of patients, the drug seems to cross the blood–brain barrier in sufficient concentration to cause these severe side effects.

Alpha-adrenergic agonists should not be used in patients taking monoamine oxidase inhibitors (MAOIs) because they may precipitate a hypertensive crisis. They are also contraindicated in patients taking tricyclic antidepressants because of an increased risk of central nervous system (CNS)-mediated depression (Schuman 2002). These drugs cause symptoms of dry mouth (and dry nose) when drained through the nasolacrimal duct into the throat.

7.1.5.4 Carbonic Anhydrase Inhibitors (CAIs)

There are at least 14 known varieties of the alpha-carbonic anhydrases (a-CA) whose main function is the hydration of CO2 to bicarbonate (HCO−). Two of these enzymes are important for the production of the aqueous humor by the epithelium of the ciliary processes, cytoplasmic CA II and membrane-bound CA IV (Matsui et al. 1996). Part of aqueous production involving active secretion relies on the formation of bicarbonate by these enzymes to correct the imbalance caused by the ATPase-fueled transport of sodium into the space between the nonpigmented ciliary epithelial cells.

Patients should be specifically asked about breathing difficulties and skin reactions (Turtz and Turtz 1958), which are the most common form of allergic manifestations to sulfonamide antibiotics.

CAIs can be used topically or systemically. Topical CAIs are remarkably free from side effect and effective. They are the most effective class to use in combination with a prostaglandin analogue (Scozzafava and Supuran 2014). Systemic CAIs are also effective, but should be used with full knowledge of the frequency and severity of their side effects.

Topical CAIs

Approximately 80 % of the volume of topically administered eyedrops is absorbed systemically within 15–30 s of instillation. Topical dorzolamide is absorbed through the nasopharyngeal mucosa into the systemic circulation. Chronic administration of dorzolamide leads to its accumulation in erythrocytes. Hepatic metabolism of dorzolamide produces N-desmethyl metabolite which also binds to red blood cells but inhibits carbonic anhydrase I more than carbonic anhydrase II. Approximately 24–32 % of systemically absorbed dorzolamide is bound to plasma proteins. Urine is the major route of excretion for both parent and metabolite drugs. There is a rapid decline of dorzolamide from red blood cells, on discontinuation of the medication. This is followed by a gradual decline due to an elimination-phase half-life of approximately 4 months.

Brinzolamide 0.1 % (Azopt, Alcon Laboratories) is a suspension that allows buffering to a more neutral pH compared with dorzolamide. This seems to improve tolerance of the topical medication.

In 2013, Simbrinza (Alcon), a beta-blocker-free, fixed-combination therapy, was approved by the FDA. It combines brinzolamide 0.1 % and brimonidine tartrate 0.2 %.

CAIs have been reported to improve ocular blood flow profile by causing ocular vasodilation through metabolic acidosis via elevated carbon dioxide levels (Siesky et al. 2008).

Oral CAIs

Oral CAIs are powerful agents for lowering IOP (between 25 and 30 %) (Friedland et al. 1977) and may do very well when other medical therapies are unable to reach the target IOP in chronic glaucomas or to temporarily bring IOP to safe levels in acute emergent situations.

Paresthesias of the fingers, toes, and nose are common with oral CAIs, less so with methazolamide at lower doses. Paresthesias may diminish over time. Patients are less likely to be concerned about these symptoms if they are discussed before the drugs are prescribed.

Patients may suffer from abdominal cramps, nausea, and in some cases severe diarrhea. Symptoms may improve as time passes, but some patients need to discontinue oral CAIs because of the gastrointestinal intolerance. The oral CAIs cause a strange metallic taste with foods and carbonated beverages – patients should be warned this is likely to occur.

Patients taking oral CAIs, usually after several months, can have an unexpected onset of a malaise-syndrome complex involving (to varying degrees) tiredness, lack of appetite (with/without weight loss), and even severe depression (Alward 1998).

Salicylates interact with oral CAIs. Patients taking high-dose aspirin can get tinnitus, increased respiratory rate, and even confusion and coma (Sweeney et al. 1986).

CAIs in the kidney promote the absorption of bicarbonate through the renal tubules. CAIs cause alkalinization of the urine along with increased micturition, both day and night, and potassium excretion. Patients prescribed with chronic oral CAIs should have their electrolytes monitored, especially if taking other potassium-wasting drugs such as thiazide diuretics and oral corticosteroids (Bateson and Lant 1973).

One important feature of both topical and oral CAIs is that they work to suppress the aqueous and lower IOP throughout the 24-h day, both in the diurnal and nocturnal time periods.

The topical CAIs lower IOP about 20 % (similar to betaxolol) and the oral CAIs closer to 30 %. Further, patients receiving a full dose of oral CAIs are unlikely to see any additional pressure lowering by also using topical dorzolamide or brinzolamide.

Acetazolamide is the most commonly used and is supplied in 125- or 250-mg tablets or 500-mg sustained-release capsules. It may be dosed up to 250 mg four times daily or 500-mg SR capsules twice a day. CAIs are not the first-line choices for treatment, despite impressive IOP-lowering effects, due to their numerous adverse effects.

The use of oral CAIs is contraindicated in patients with a history of kidney stones or other renal disease, liver disease, cardiac disease, Addison's disease, and severe chronic obstructive pulmonary disease and in patients with sulfonamide allergy out of concern for sulfa cross-reactivity.

7.1.5.5 Miotics

The parasympathomimetic medications are the oldest form of eyedrops used to treat glaucoma. Since they all act on the iris sphincter muscle to make the pupil smaller, we shall use the simpler name "miotics" when referring to these agents. The miotics are subdivided into two classes based on mechanism of action, the *direct*-acting cholinergic agents like pilocarpine and carbachol and the *indirect*-acting anticholinesterase agents like echothiophate iodide.

Only ocular cholinergic agent used for therapeutic purpose these days is pilocarpine. It is available at 1–4 % solution for clinical use as nitrate or hydrochloride salt.

Pilocarpine lowers the IOP by constricting the ciliary body muscles that are connected to the scleral spur to open the trabecular meshwork mechanically and increase the outflow of the aqueous humor through the conventional drainage pathways. It has been demonstrated by Worthen that pilocarpine treatment reduces the diurnal variation of IOP of patients with glaucoma as well as lowers the mean IOP (Worthen 1976).

Pilocarpine penetrates the cornea well (Quigley and Pollack 1977). While the kinetics and distribution of pilocarpine within the eye have been studied, the exact

mode by which the drug metabolizes is not fully understood. Enzymatic hydrolysis of pilocarpine, which occurs in the serum and liver, may not be an important factor in the eye. The relatively prolonged action of pilocarpine may be related to storage of the drug in ocular tissues. Van Hoose and Leaders have suggested that pilocarpine may be stored within the cornea, which may then serve as a drug reservoir (Van Hoose and Leaders 1974).

According to traditional teaching, pilocarpine needs to be instilled four times a day as its duration of action is 6 h, but a study has shown that even pilocarpine 2 % administered twice daily can lower IOP effectively in many patients with glaucoma.

Local side effects of these miotic agents include miosis, increased lacrimation, induced accommodation, and browache (Zimmerman and Wheeler 1982). Induced near accommodation (myopia) is particularly troublesome to young, phakic patients, especially with the waxing and waning of accommodation every 4–6 h given the normal QID dosing of drugs like pilocarpine. But miotics work fine in pseudophakes. Miotic agents can disrupt the blood–brain barrier and should not be used chronically in patients with ocular inflammation.

Although pilocarpine may be helpful for breaking an acute attack of angle-closure glaucoma, by causing miosis and pulling the mid-dilated pupil away from the lens it is blocking, stronger concentrations of pilocarpine may aggravate rather than help papillary block. The 4 % concentration of pilocarpine may move the lens–iris diaphragm too far forward.

It is better to use no more than 2 % pilocarpine when treating a patient with acute angle closure and pupillary block. Further, if IOP is over about 40 mmHg, the iris sphincter muscle is ischemic and hence cannot contract in response to pilocarpine. Thus, there is little benefit of this agent until the pressure can be reduced by topical beta-blockers, brimonidine, topical CAIs, oral CAIs, oral hyperosmotics, or emergent paracentesis.

Chronic use of any of the miotics may lead to the formation of posterior synechiae, leading in rare cases to an occluded pupil. Highly myopic patients may suffer retinal tears or detachments with the stronger concentrations of miotic agents (Pape and Forbes 1978).

Systemic side effects of the parasympathomimetic agents include crampy gastrointestinal upset, diarrhea, increased salivation, and increased secretion of stomach acid.

Because cholinesterase activity is suppressed by the indirect-acting miotics, succinylcholine should not be administered to patients undergoing anesthesia until at least 6 weeks after ceasing these glaucoma drugs (Eilderton et al. 1968). Today, miotic agents for glaucoma are used more as the exception (boutique use) rather than as the rule. They may be helpful in select patients when no other combination of medications can bring the patients' disease under control.

7.1.5.6 Hyperosmotic Agents

Hyperosmotic agents are generally used for short-term IOP control in emergency situations where other medications are unable to lower the IOP (Singh 2005). Intravenous (IV) mannitol and oral glycerins (or glycerol) are the most commonly

used hyperosmotic agents. Both agents penetrate the blood–ocular barrier poorly, which is a definite advantage, since this fact creates a larger osmotic gradient for water to follow.

Mannitol

Mannitol can be given either as an IV infusion using a 20 % premixed solution (concentration of 200 mg/ml) at a dose of 1–2 g/kg of body weight.

Because of the limited solubility, storage at room temperature (25 °C) is recommended. Mannitol solutions commonly crystallize at low temperatures. If crystallization occurs, the solution should be warmed prior to use. Mannitol should not be administered if crystals are present.

Mannitol should be administered intravenously over 30–60 min. Too rapid an infusion of mannitol will cause a shift of intracellular water into the extracellular space, resulting in cellular dehydration with a high risk of hyponatremia, congestive heart failure, and pulmonary edema. Slow administration, over at least 20–30 min, may also avoid transient increases in cerebral blood flow that may exacerbate or increase intracranial bleeding in predisposed patients. Doses in excess of 200 g IV mannitol/day have been associated with acute renal failure.

Glycerin (or Glycerol)

Glycerol is usually used as a 50 % oral solution at a dose of 1–1.5 g/kg of body weight (McCurdy et al. 1966). Because of its unpleasantly sweet taste, it is often given with juice or over ice. The onset of effect can occur within 10 min, with a peak effect at approximately 1 h. The duration of action is 4–5 h. In elderly patients, the minimum dose (e.g., 1 g/kg) required to produce the desired effect should be used to avoid serious side effects.

Because hyperosmotic agents increase the extracellular space, they may precipitate pulmonary edema and cardiac failure in patients with compromised cardiac function.

7.2 Concept of Neuroprotection in Glaucoma

As glaucoma is characterized by a progressive optic neuropathy, it seems logical to try to find the “holy grail of neuroprotection” as do the neurologists for the neurodegenerative diseases of the brain and the nerves (Danesh-Meyer and Levin 2009; Chang and Goldberg 2012).

In our current management of glaucoma, we are only aiming to limit the impact of some risk factors that lead to the acceleration of RGC death. The most

documented and most modifiable risk factor is IOP. Many studies in the last two decades have shown the effectiveness of decreasing IOP in several glaucoma types (Collaborative Normal-Tension Glaucoma study group 1998; AGIS 2000; Leske et al. 2003). Unfortunately some risk factors such as family history, aging, myopia, and ethnicity are not accessible to any treatment. Therefore it makes sense to concentrate on the final effect of these risk factors, namely, RGC loss (Osborne 2008).

Most of the attention of the researchers has been focused on neurons; however, neurons are strongly connected to their environment such as glia, vessels, and connective tissue, and all these components are potential targets for neuroprotection (Shih and Calkins 2012). Several pathogenic pathways are now clearly identified such as inflammation, immunity, neurotrophin deprivation, excitotoxicity, oxidative stress, mitochondrial dysfunction, etc. (Limb and Martin 2011).

There is a body of evidence to consider that neuroprotection in preclinical studies does work. Unfortunately we do not have a perfect animal model for glaucoma, and it is true that the models we are currently using do not mimic closely the human course of glaucoma (Quigley 2012). Therefore translational research from the lab to humans requires a lot of care and humility. More information on the pathogenesis of RGC death and preclinical studies can be found in several reviews (Baltmr et al. 2010; Osborne et al. 1999b). In this text we will only report two clinical trials in humans, one with a topical agent and one with a drug taken orally.

7.2.1 Brimonidine

Brimonidine has been evaluated as a neuroprotectant in three human clinical trials. In nonglaucomatous optic neuropathies, its efficacy was not demonstrated either in Leber hereditary optic neuropathy or in anterior ischemic optic neuropathy (Newman et al. 2005; Wilhelm et al. 2006).

The Low-Pressure Glaucoma Treatment Study (LoGTS), a multicenter double-masked randomized trial, evaluated the long-term visual field stability in patients with normal-tension glaucoma treated with brimonidine or timolol (Krupin et al. 2011). In the group treated with brimonidine, progression was less frequent than in the group receiving timolol. These results have been intensively discussed, and like in every clinical trial, some weaknesses were highlighted (Cordeiro and Levin 2011). Among the 178 analyzed patients, 9.1 % on brimonidine and 39.2 % on timolol progressed during a mean follow-up of 30 months. However many patients (20 %) discontinued the treatment in the brimonidine arm due to allergy, and the high rate of progressing patients on timolol could suggest that this beta-blocker is deleterious to retinal ganglion cells which has not been fully documented yet (Hare et al. 2004a, b). Anyway this study is probably the first trial showing a potential protective effect of a drug in a well-designed and conducted study.

7.2.2 *Memantine*

Memantine, an NMDA glutamate receptor antagonist, has shown some neuroprotective properties in laser-induced glaucoma in monkeys (Hare et al. 2004a, b; Reisberg et al. 2003). It was the first drug approved as a neuroprotective agent in moderate-to-severe Alzheimer's disease (Osborne 2009). Memantine, a widely available drug, has been evaluated in glaucoma patients, with a two parallel, double-masked, placebo-controlled three-armed phase III study. More than 1000 patients were recruited in 89 centers, and the primary end point progressive visual field loss was confirmed. There was a slower disease progression in patients receiving the higher memantine dose versus the lower dose and placebo. Unfortunately the results were never published in the scientific literature, and we are still wondering what can be taught from this study for the future (Osborne 2009; Sena and Lindsley 2010).

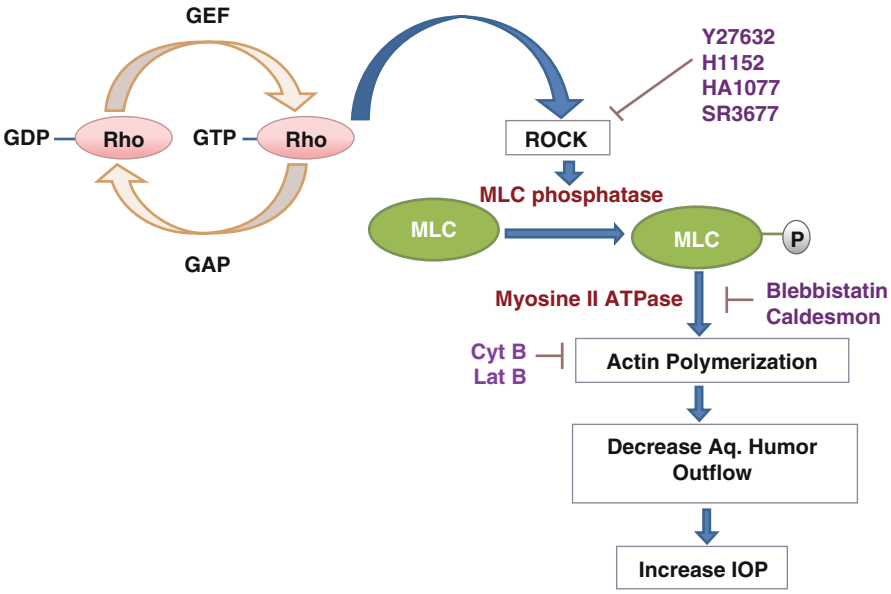
Neuroprotection is a fascinating area for research although a recent Cochrane review was not able to report any robust study showing the positive effect of a neuroprotective drug (Levin and Danesh-Meyer 2010). Researchers and companies have made tremendous efforts and spent a lot of money until now without practical and clinical results. Neville Osborne nicely defended the idea that although until now we have been disappointed by all the attempts to master and delay the degeneration of RGCs, it is not a good reason to abandon the fight against glaucoma-related blindness (Wang and Chang 2014). It is often taught in medical school that the first pioneer to operate cerebral tumors, Cushing, was faced with the death of his first ten patients. Hopefully for the future, he did not give up. So if we are not here yet with neuroprotection today, let's continue the fight against RGC degeneration, just keeping in mind that a major hurdle is the translation from basic research to clinical application (Wang and Chang 2014).

7.3 Newer Drug Classes

7.3.1 *Rho-Kinase and Glaucoma*

Rho-associated protein kinase (ROCK) plays an important physiological role in smooth muscle contraction and has been studied as a target for a variety of diseases. Substantial evidences with ex vivo, in vitro, and animal models showed that ROCK inhibition showed relaxation of tissues in the conventional outflow pathway and lower intraocular pressure and may represent a new treatment modality for POAG. Rho is a small GTPase that is involved in the regulation of many cell processes including contraction, cytoskeleton organization, adhesive interactions, trafficking, and permeability. Activation of the Rho/Rho-associated kinase (ROCK) pathway is activated via secreted bioactive molecules or via integrin activation after extracellular matrix binding. These lead to polymerization of actin stress fibers and formation of focal adhesions. This pathway has been demonstrated to increase the

resistance to aqueous humor outflow through the trabecular meshwork pathway by inducing alterations in cell contraction, actomyosin assembly, cell adhesion, and ECM synthesis. Inhibition of ROCK pathway leads to decrease in flow resistance and increase in aqueous humor outflow and thus has a potential role in glaucoma therapy. The schematic representation for Rho-ROCK signaling is given below:



7.3.1.1 Rho-Kinase Inhibitors

Multiple studies have demonstrated that inhibition of ROCK and Rho GTPase would be an attractive strategy to increase aqueous humor drainage in TM tissues leading to reduction in IOP (Rao and Epstein 2007; Challa and Arnold 2014; Tanihara et al. 2008). These drugs reduce IOP by increasing aqueous humor outflow facility through actomyosin regulation. Several drugs have been developed over the past decade; however, only four drugs such as K-115, AR-13324, PG324, and AMA 0076 showed promising clinical efficacy in clinical trials. The only minor side effect with ROCK inhibitors is conjunctival hyperemia. On systemic level, ROCK inhibition is known to lower blood pressure and vascular resistance thus bearing potential consequences in case of unwanted systemic exposure (Hahmann and Schroeter 2010).

K-115: This compound is in the development by the Japanese company, Kowa Pharmaceuticals. In phase II randomized dose–response study, this compound lowered IOP by 3.1 mmHg 8 h after instillation which is comparable to prostaglandin analogues. This drug has now advanced to phase III trials, and it is anticipated that this drug will be used either as monotherapy or in combination with prostaglandins

and beta-blockers. Conjunctival hyperemia, the most commonly reported adverse effect of ROCK inhibitors, occurred in 65.3% with the optimal dose.

ROCK inhibitors in the pipeline: Several Rho-kinase inhibitors are now in earlier stages of clinical testing.

AR-12286: Aerie Pharmaceuticals is developing a novel selective ROCK inhibitor which showed a statistically significant dose-dependent reduction in mean IOP with peak effects occurring 2–4 h after dosing in phase II trials with humans. The largest IOP reduction (−6.8 mmHg) was noted with 0.25 % w/v concentration of AR-12286 following twice-daily dosing. The 0.25 % w/v concentration produced trace to moderate conjunctival hyperemia that was transient and occurred in less than 10 % of patients with once-daily dosing.

The other compound of this series is **AR-13324** which is in phase IIb study in clinical trials. This molecule has been developed with a dual mechanism of action to lower IOP: one is to enhance the fluid outflow through trabecular pathway and the other is to decrease fluid inflow to the eye.

AMA0076: This compound has been developed by the Belgian company, Amakem Therapeutics, which showed to act on the trabecular meshwork where it relaxes the smooth muscle to widen the outflow channels. It has been designed to convert rapidly to inactive form to prevent off-target activity and reduce hyperemia.

7.3.2 Nitric Oxide-Donating Latanoprost

VESNEO™ (latanoprostene bunod; previously known as BOL-303259-X and NCX 116) is a novel nitric oxide-donating prostaglandin F2 alpha analogue licensed by Nicox to Bausch + Lomb. The pivotal phase 3 program includes two separate randomized, multicenter, double-masked, parallel-group clinical studies, APOLLO and LUNAR, designed to compare the efficacy and safety of VESNEO™ administered once daily (OD) against timolol maleate 0.5 % administered twice daily (BID) in lowering IOP in patients with open-angle glaucoma or ocular hypertension (Yang and Leffler 2013).

7.4 Newer Delivery Systems

Drug delivery systems currently being developed include conjunctival, subconjunctival, and intravitreal inserts, punctal plugs, and drug depots.

A hybrid dendrimer hydrogel/poly(lactic-co-glycolic acid) nanoparticle platform is being designed to release the drug slowly, and it is compatible with many of the currently used glaucoma drugs (Fulgencio et al. 2012).

A timolol maleate-loaded chitosan film has been recently found to be safe and efficient as an ocular drug delivery system in the treatment and prevention of

glaucoma (Fulgencio et al. 2012). Chitosan is a cationic polysaccharide biopolymer with mucoadhesive properties.

Other alternatives used for extended drug release include particulate drug delivery systems or injectable formulations such as microspheres, liposomes, and nanospheres/nanoparticles (Manickavasagam and Oyewumi 2013). The drug is trapped in the nanocarrier matrix and delivered into the eye. After administration, the bioactive agent is released in a controlled fashion by diffusion through the matrix or by degradation of the polymer matrix. Additionally, once the nano/micro-carriers are injected, they can act as a reservoir system for drug release for a prolonged time period.

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