Clinical Medicine Reviews in Therapeutics

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REVIEW

Emerging Therapeutic Regimens for Glaucoma and Ocular Hypertension

Pankaj Kumar Agarwal[1], Lik Thai Lim[2] and Donald Montgomery[3]

[1]Princess Alexandra Eye Pavilion, Edinburgh, [2]Tennent Institute of Ophthalmology, Glasgow, [3]Glasgow, Royal Infirmary, Glasgow, United Kingdom. Corresponding author email: p.agarwal1@nhs.net

Abstract: Glaucoma is the name given to a group of diseases characterized by incurable, progressive, multifactorial optic neuropathy. It is the second leading cause of blindness worldwide. Ocular hypertension (OH) is the term used to describe the presence of raised intraocular pressure (the most important risk factor for the development of glaucoma) in the absence of demonstrable glaucomatous optic neuropathy.

The management of glaucoma and OH requires a holistic and rational approach, taking into account a number of factors. Treatment needs to be individualized depending on patient age, the severity and type of glaucoma, associated medical conditions, the condition of the ocular surface, tolerability of topical medication, and patient wishes. An understanding of the mechanism of glaucoma and its etiology in a particular patient is crucial for the initiation of appropriate treatment.

This review article summarizes the existing medical management of glaucoma and OH, including pharmacology, mode of action, and safety profile for each major group of medication, and reviews current advances and future developments in treatment for glaucoma, including experimental medications, together with a summary of their modes of action, pharmacology, and safety profiles. It is hoped that readers will become more aware of the evolution of the next generation glaucoma and OH medications.

Keywords: glaucoma, hypertension, therapy

Clinical Medicine Reviews in Therapeutics 2012:4 1–12

doi: 10.4137/CMRT.S3236

This article is available from http://www.la-press.com.

Introduction

Glaucoma is the name given to a group of diseases characterized by incurable, progressive, multifactorial optic neuropathy. It is the second leading cause of blindness worldwide.[1–3] Ten percent of patients with glaucomatous optic nerve damage will suffer visual impairment and blindness[1] which is associated not only with increased morbidity but also with increased mortality.[2] Ocular hypertension (OH) is the term used to describe the presence of raised intraocular pressure (IOP, the most important risk factor for development of glaucoma) in the absence of demonstrable glaucomatous optic neuropathy.

Upon diagnosis, the management of glaucoma requires a holistic and rational approach, taking into account a number of factors. Treatment needs to be individualized depending on patient age, the severity and type of glaucoma, associated medical conditions, the condition of the ocular surface, tolerability of topical medication, and patient wishes. An understanding of the mechanism of glaucoma and its etiology in a particular patient is crucial for the initiation of appropriate treatment.

Published guidelines of the European Glaucoma Society[4] define the goal of glaucoma treatment as follows: "The preservation of visual function adequate to the individuals needs with minimal or no side effects, for the expected lifetime of the patient without any disruption of his/her normal activities at a sustainable cost." In the pursuit of this goal, the clinician may choose from four options, ie, no therapy, medical therapy, laser, and surgery. There are potentially three areas which can be targeted to delay or prevent progression of glaucoma. These are reduction of IOP, regulation of ocular blood flow, and neuroprotection. Currently, lowering of IOP is the only proven effective approach for preserving visual function[5,6] and this is usually achieved initially with medical therapy. Over the past 30 years, the medical armamentarium has expanded greatly to include a number of efficacious and generally well tolerated medications. However, the search continues for safer and more effective products. This paper reviews the drugs currently in use before describing some of the novel agents in various stages of development and evaluation.

Case for Lowering IOP

Medical treatment has been shown in numerous studies to be beneficial in patients with glaucoma and OH.[7–14] The Ocular Hypertension Treatment Study[15] showed that patients with OH on treatment who achieve a mean drop in IOP of 22% have a 4.4% risk of progression to glaucoma over five years compared with 9% without medication. This is an approximate 50% reduction in risk of progression to glaucoma with a 22% reduction in IOP. The inference from this study was that topical medication is effective in delaying or preventing the onset of glaucoma in patients with high IOP. This does not mean that all patients with borderline high IOP should receive medication. Only individuals who are at moderate or high risk of developing glaucoma should be treated. The study identified the following risk factors as being associated with increased risk of disease progression: older age, vertical and horizontal cup-to-disc ratios $> 0.4–0.5$, IOP > 26 mmHg and, importantly, a central corneal thickness < 555 µm. Treatment of OH should only be initiated if the risk of progression to sight-threatening glaucoma is assessed as outweighing the potential adverse effects of treatment with regard to the patient's quality of life. Lowering IOP in elderly patients or in those in whom the disease is very slowly progressive may not be necessary if the disease is unlikely to affect them during their lifetime.

Where glaucomatous neuropathy is already established, treatment is usually justifiable except where life expectancy is very limited. A number of landmark studies[7–15] suggested that, especially in advanced glaucoma, IOP reduction of at least 30% should be sought. However, with currently available drugs, this is often unachievable with a single medication and many patients therefore require use of multiple drops or fixed-combination treatments. The more drops patients have to use the less likely they are to be compliant with medication.

Current Treatment Options

The IOP-lowering efficacy and side effect profiles of currently available medications are summarized in Table 1. It is clear that all of these treatments have shortcomings and that there is a need for better agents that target glaucoma more specifically and more potently without incurring adverse effects. A number of novel agents are now under development and evaluation. Some of these agents aim to improve IOP-lowering efficacy while minimizing the risk of adverse effects. The efficacy of a medication can be enhanced if it targets

Table 1. Summary of currently available topical ocular antihypertensive medications.

Topical ocular antihypertensive medications	Mechanism of action	Potential side effects
Cholinergic agents (eg, pilocarpine)	Stimulates muscarinic receptors in the sphincter pupillae and ciliary body. Increases trabecular outflow via ciliary muscle contraction plus some minor decrease in aqueous production.	Ciliary muscle spasm, brow ache, accommodative myopia, miosis with constriction of visual fields, increased risk of retinal detachment, aqueous barrier instability, keratopathy, hypersensitivity, exacerbation of uveitis, bradycardia, nausea, sweating, bronchospasm.
Beta-blockers (eg, timolol)	Reduces aqueous secretion by inhibitory action on beta-adrenoceptors in the ciliary body. Estimated to reduce IOP by 27%.[70]	Ocular surface irritation, bronchospasm, exacerbation of heart failure, nightmares. Contraindications: asthmatics and patients with heart failure.
Prostaglandin analogs (eg, latanoprost)	Increases aqueous outflow by the uveoscleral route. Estimated to reduce IOP by 30%.[70]	Conjunctival hyperemia, iris discoloration, bitter taste.
Carbonic anhydrase inhibitors (eg, dorzolamide)	Reduces aqueous secretion by the ciliary body. Estimated to reduce IOP by 20%.[70]	Ocular irritation, allergic reaction, paresthesia.
Adrenergic receptor agonists (eg, epinephrine)	Decreases aqueous outflow and later increases uveoscleral outflow and trabecular outflow. They are additives with miotics and carbonic anhydrase inhibitors.	Reactive conjunctival hyperemia, burning/stinging, adrenochrome deposits, madarosis, mydriasis, maculopathy, elevated blood pressure, tachycardia, arrhythmias, headache, anxiety.
Alpha 2 agonists (eg, brimonidine)	Reduces aqueous production. Estimated to reduce IOP by 21%.[70]	High rate of allergy, conjunctival hyperemia/blanching, follicular conjunctivitis (10%), subsensitivity, dry mouth, systemic blood pressure reduction (never use in children), fatigue and drowsiness, avoid with monoamine oxidase inhibitors (antidepressants) because it may cause serious systemic reactions.
Prostamides (eg, bimatoprost)	Increases aqueous outflow by the uveoscleral route. Estimated to reduce IOP by 30%.[70]	Conjunctival hyperemia, iris discoloration, bitter taste.

both aqueous production and outflow. Others aim to promote neuroprotection or improve optic nerve perfusion. Even methods of intervening in genetic mechanisms for some types of glaucoma are being explored.

A significant effort is being made to improve the existing classes of drugs. The aim is to decrease the side effects of some of the most successful drugs used in the treatment of glaucoma, namely prostaglandin analogs and prostamide. The most common side effects of this group of drugs are conjunctival hyperemia, increased iris pigmentation, and periorbital hyperpigmentation. These side effects could be prevented if a prostaglandin analog could be developed with selective activity towards the ciliary muscle cells to reduce IOP effectively whilst having no activity towards the conjunctival or iris blood vessel receptors, and thus preventing hyperemia. Prostamide has the advantage over latanoprost in this regard, with the incidence of hyperemia being 1% after two years compared with 30%, respectively.[16,17] The following are the novel drugs which are currently being investigated for use in OH and glaucoma.

Drugs Under Investigation

Prostaglandin FP receptor agonists

These are an addition to the numerous drops available but may not offer significant improvements over existing drugs. The mechanism of action exclusively involves pressure-independent increases in uveoscleral outflow (as shown in primate studies).[18] The following prostaglandin FP receptor agonists are currently being investigated.[18,19]

Table 2. Summary of new prostaglandin analogues currently under development.[18]

Name	Patent	Year	Inventors	Assignee
Cyclopentane 1-hydroxyl alkyl, alkenyl-2-one α-hydroxy derivatives	US6248783	2001	Burk RM, et al	Allergan
11-aza analog formulation	US6211226	2001	Hellberg MR, Klimko PG	Alcon
Cloprostenol and fluprostenol analogs	US6184250	2001	Klimko PG, et al	Alcon
Macrocyclic 1,15 lactones of fluprostenol and related prostaglandin F2α analogs.	W02001057015	2001	Maxey KM Stanton ML	Cayman Chemical
F-type prostaglandins	US6124344	2002	Burk RM	Allergan
2-decarboxy-2-phosphofinico prostaglandin F analogs	US6372730	2002	Delong MA, et al	Procter and Gamble
13-aza prostaglandins	US6417228	2002	Klimko PG	Alcon
15-keto-latanoprost	W02002007731	2002	Ueno R	Sucampo AG
Cyclopentane heptan(ene)ioc acid, 2-heteroarylalkenyl derivatives	US6602900	2003	Burk RM	Allergan

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Prostaglandin EP2 receptor agonists

These are useful in the treatment of OH and neurodegeneration associated with glaucoma. The mechanism of action is similar to that of prostaglandin FP receptor agonists as described above.[18]

The patent for medical use of the prostaglandin EP2 receptor agonist is held by Allergan. The list of relevant patent applications relating to agents evaluated in this class is shown in Table 3.

Prostaglandin EP4 receptor agonists

These are showing promise in lowering IOP, with effects demonstrated in nonhuman primates. The IOP is lowered by increasing the pressure-dependent outflow facility of the eye.[18] The mechanism of action of prostaglandin EP4 receptor agonists is different from that of other prostaglandin analogs. One of the early forms, ie, 3,7-dithia PGE_1, lowers IOP by increasing the pressure-dependent outflow facility. The following is a list of patent applications relating to agents evaluated in this class. (see Table 4).

Prostamides

Prostamides have been available since the turn of the 21st century, with bimatoprost being a prominent example of a synthetic analog of prostamide F2α. It has been shown to be more potent than prostaglandin FP receptor agonist prodrugs in reducing IOP, making it the most effective IOP-lowering agent of its kind.[20,21] It can also be effective in patients whose response to latanoprost is poor. A number of new compounds in this drug class are currently being developed in the hope of out-performing bimatoprost.[22,23]

Rho kinase inhibitors

Rho-associated coiled coil-forming protein kinase (ROCK) inhibitor has been shown to reduce IOP in Phase I clinical investigations. ROCK has been

Table 3. Summary of prostaglandin EP2 receptor agonists currently under development.[18]

Title	Patent	Year	Inventors	Assignee
Nucleic acid encoding a human EP prostaglandin receptor	US6395878	2002	Regan JW, et al	Allergan
Preparation of pyrazolidinones as ligands of the prostaglandin EP2 and EP4	W02003035064	2003	Araldi GL, et al	Applied Research Systems ARS Holding NV
8-azaprostaglandin analogs	US6573294	2003	Old DW, et al	Alcon
Thiophenes and furans as prostaglandin analogue	W02004012656	2004	Burk RM, et al	Allergan
Ω-cycloalkyl-17-heteroaryl-prostaglandin E2	US6710072	2004	Burk RM, et al	Allergan

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Table 4. Summary of prostaglandin EP4 receptor agonist currently under development.[18]

Title	Patent	Year	Inventors	Assignee
γ-lactams	W02003103604	2003	Araldi GD, et al	Applied Research Systems ARS Holding NV
Asparagine-derived 1,5-disubstituted imidazolin-2-one derivative	W02003103664	2003	Billot X Young RN	Merck Frost Canada
2-pyrrolidinone derivative as selective EP_4 receptor agonist	W02004037786	2004	Billot X, et al	Merck Forrest, Canada
Oxazolidine-2-one and thiozolidine-2-one derivatives	W02004019938	2008	Han Y, et al	Merck Forrest, Canada
8-azaprostaglandin derivatives	W02004065365	2004	Kambe, et al	Ono Pharmaceutical
Piperidinyl prostaglandin E analogs	US6747037	2004	Old DW, Dinh TD	Allergan
3-oxa-8-azaprostaglandin analogs	US6734206	2004	Old DW	Allergan
Substituted benzoic acid	W02005116010	2005	Belley M, et al	Merck Forrest, Canada
Cyclohexyl prostaglandin analogs	US2005049227	2005	Old DW	Allergan
2,3,4-substituted cyclopentenones	US20060111430	2006	Donde Y, et al	Allergan

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shown to be present in ocular tissues, including trabecular meshwork and ciliary muscles. Inhibition of ROCK activity has been shown to induce alterations in trabecular meshwork cellular responses, such as migration, adhesion, and changes in cell shape, which in turn improve aqueous outflow, thus reducing IOP. A Phase 1 clinical study showed that after topical ocular instillation of a ROCK inhibitor, the IOP-lowering effect was at its peak at 2–4 hours, after which the IOP gradually climbs back up to baseline. The safety profile of this experimental drug was good, with no reported systemic side effects. Local side effects are tolerable, most commonly mild hyperemia of the bulbar and palpebral conjunctiva. The following is a list of patent applications relating to agents in this class that have undergone evaluation. (see Table 5).[24]

Cannabinoids

Cannabinoids like marijuana (active ingredient tetrahydrocannabinol) have been demonstrated to lower IOP.[25,26] However, due to the short half-life and myriad systemic side effects of marijuana, its development into useful IOP-lowering agents has not progressed.[27] Adverse effects are local redness and irritation and a

Table 5. Summary of Rho kinase inhibitors currently under development.[18]

Title	Patent	Year	Inventors	Assignee
Prevention/remedies containing Rho kinase inhibitors for treatment of glaucoma	W02000009162	2000	Azuma M, et al	Senju Pharmaceuticals; Yoshitomi Pharmaceuticals
Preparation of amides as Rho kinase inhibitors	JP2003073357	2003	Uehata, et al	Mitsubishi Pharmaceutical
Preparation of pyrazinamine and pyridinamine derivatives	W02005003101	2005	Birault V, Harris JC	Biofocus Discovery
Olefin derivatives	W20050035503	2005	Hagihara M, et al	Ube Industries Santen Pharmaceutical
Isoquinoline derivatives	W02005035503	2005	Hagihara M, et al	Ube Industries Santen Pharmaceutical
Indazole compounds	W02005035506	2005	Hagihara M, et al	Ube Industries Santen Pharmaceutical
1,6,7 trisubstituted azabenzimidazoles	W02005034866	2005	Lee D, Stravenger RA	Glaxo Group
Aminofuran-2-amyul imidapyridines	W02005037197	2005	Lee D, et al	Glaxo Group
1,7 disubstituted azabenzimidazoles	W02005037198	2005	Lee D, et al	Glaxo Group
Diazaphenalene derivatives	W02001028498	2006	Yamada R, Seto M	Asahi Kasei Pharmaceuticals

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Table 6. Summary of new cannabinoids currently under development.[18]

Title	Patent	Year	Inventors	Assignee
Retro-anandamide, high affinity and stability cannabinoid receptor ligands.	WO2001028498	2001	Makriyannis A, et al	University of Connecticut
Pharmaceutical compounds, particularly tetrahydronaphthalene ester, amide and tetrazolederivatives, useful as modulators of endocannabinoid mediated response.	WO2002024630	2002	Cullinan GJ, et al	Eli Lilly
Bicyclic pyrimidinyl derivatives and methods of use thereof.	US2003139427	2003	Castelhano AL	OSI Pharmaceuticals
Synthetic analogs of endogenous cannabinoids, preparation and therapeutic use thereof.	US6531636	2003	Mechoulam R, et al	Yissum Res Dev
Preparation of heteroarene derivatives as cannabinoid receptor agonists.	US20044044051	2004	Kozlowski JA, et al	Schering
Delta-9-tetrahydrocannabinoid solution metered dose inhalers and methods of use.	US6713048	2004	Peart J, et al	Virginia Commonwealth University
Preparation of cannabimimetic indole derivatives with cannabinoid CB1 or CB2 receptor binding affinity.	US6900236	2005	Makriyannis A, Deng H	University of Connecticut
Novel bicyclic cannabinoid agonists for the cannabinoid receptor	US6943266	2005	Makriyannis A, Khanolkar A	University of Connecticut
Preparation of 2,3-dihydrobenzofuran and 2,3-dihydrobenzothiophene derivatives as cannabinoid receptor modulators.	WO2005000829	2005	Ohkawa S, et al	Takeda Pharmaceutical
Preparation of biphenyl derivatives and analogs thereof, as cannabinoid receptor ligands and methods of use.	US2006074086	2006	Dolle RE, et al	Adolor
Dibenzopyranone derivative peripheral cannabinoid receptor (CB2) selective ligands, their preparation and therapeutic use.	US6995187	2006	Makriyannis A, Khanolkar A	University of Connecticut

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psychotropic effect. A number of different agents in this class have been the subjects of investigation and patent application as listed in Table 6.

Serotonergics

The serotonin receptor ($5HT_2$) agonists have been shown to lower IOP in nonhuman primates. The exact mechanism of action has not been elucidated but it is thought that these modulate aqueous humor dynamics, thus lowering IOP. Many different potential drugs in this class have been under investigation. However, development of these is still in its infancy (Table 7).[28]

Bioenergetic Therapies

This new area of research revolves around the theory that mitochondrial dysfunction can contribute towards neurodegeneration of retinal ganglion cells in glaucoma. This idea arises from the fact that similarities between glaucoma and mitochondrial optic neuropathies had previously been observed, with retinal ganglion cell loss being a common feature. Due to structural and energetic constraints, the retinal ganglion cell is susceptible to mitochondrial dysfunction. Age also plays a role in declining mitochondrial function. Early research has slowly opened up a new approach to slow down or halt glaucomatous neurodegeneration by finding ways to increase mitochondrial biogenesis or improving quality control in the mitochondrial life cycle.[29]

RNA Nucleotides

New substances linked to the nervous system that innervate the eye are emerging as interesting candidates to reduce IOP. Nucleotides, commonly costored with catecholamines or acetylcholine or the indole, melatonin, show interesting properties in reducing IOP. Moreover, new technological ideas such as the use of small interference RNA to silence protein expression demonstrate the relevance of

Table 7. Summary of serotonergics currently under development.[18]

Title	Patent	Year	Inventor	Assignee
1-aminoalkyl-1H-indoles for treating glaucoma.	WO2001040183	2001	Chen HH, et al	Alcon
Compounds with $5HT_2$ and $5HT_{1a}$ agonist activity for treating glaucoma.	WO200170223	2001	Collier RJ, et al	Alcon
Preparation of 2-acylaminobenzimidazoles for treating glaucoma.	WO2001070705	2001	Rusinko A, et al	Alcon
Novel arylaminopropane analogs, particularly naphthylaminopropane derivatives, with 5HT receptor activity, and their use for lowering IOP in the treatment of glaucoma.	WO2002098400	2002	Hellberg MR, Namil A	Alcon
New combination of serotonin $5HT_{2c}$ agonist and $5HT_6$ antagonist as pharmaceutical formulation and therapeutic uses.	WO2002008178	2002	Sukhwinder J, et al	Biovitrum AB
Preparation of novel benzodifuranimidazolines and benzofuranimidazolines for the treatment of glaucoma.	WO2003053436	2003	Feng X, Hellberg ME	Alcon
Substituted 5-hydroxyindole compounds for the treatment of glaucoma.	WO2003051291	2003	May JA, Dantanarayana AP	Alcon
Ophthalmic pharmaceuticals containing serotonergic $5HT_2$ agonist for treating glaucoma.	US6664286	2003	May JA, et al	Alcon
Beta-hydroxyphenylalkylamines and their use for treating glaucoma.	WO2004028451	2004	Glennon RA, Hellberg MR	Virginia Commonwealth University
A preparation of novel benzopyran analogs, useful for the treatment of glaucoma.	WO2004054572	2004	Hellberg MR, Hamil A	Alcon
Substituted 5-chroman-5-ethylamines for the treatment of glaucoma.	WO2004019874	2004	May JA, Dantanarayana AP	Alcon
Pyranoindazoles with $5HT_2$ receptor activity, and their use for lowering IOP in the treatment of glaucoma.	US6881749	2005	Chen HH, et al	Alcon
Substituted furo[2,3-g]indazoles with $5HT_{2a}$ receptor activity, and their use in lowering IOP in the treatment of glaucoma.	WO2005053688	2005	Dantanarayana AP, May JA	Alcon
Preparation of substituted [1,4]oxazino [2,3-g]indazoles for the treatment of glaucoma.	US2005130960	2005	Dantanarayana AP, May JA	Alcon
Preparation of duhydroimidazo[2,1-b]thiazole and dihydro-5H-thiazolo[3,2-a]pyrimidines as antidepressant agents.	US6900216	2005	Doyle KJ, et al	Knoll GmbH
$5HT_2$ agonists for controlling IOP and treating glaucoma.	US6927233	2005	May JA, Dantanarayana AP	Alcon
Preparation of benzindazoles and indenopyrazoles for treatment of glaucoma.	US6933392	2005	May JA, Zinke PW	Alcon
Preparation of 1-(2-aminoethyl)-6-hydroxyindazoles for treating glaucoma.	US6956036	2005	May JA, et al	Alcon
Novel fused indazoles and indoles with $5HT_2$ receptor activity and their use for lowering IOP in the treatment of glaucoma.	US6960608	2005	May JA, Dantanarayana AP	Alcon
Preparation of piperazinylpyridine derivatives as $5HT_3$ receptor antagonists, pharmaceutical compositions containing them and their uses.	JP2005225845	2005	Sato M, et al	Teikoku Hormone Manufacturing
Use of N-desmethylclozapine to treat human neuropsychiatric disease.	US2005250767	2005	Weiner DM, Brann MR	Acadia Pharmaceutical
Preparation of substituted 3-(2-aminopropyl)-5-hydroxy-indazoles and related compounds for treating glaucoma.	US7005443	2006	May AJ, Feng X	Alcon

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this method to approach OH and glaucoma from a different point of view. The three main groups of molecules, ie, nucleotides, melatonins, and small interference RNAs, each show promise as candidates for the treatment of OH and glaucoma in the near future.[30]

Nucleotides and dinucleotides of varying compounds exist in the aqueous humor of the eye. Depending on the compounds, some nucleotides increase IOP while others decrease it when administered topically. Those showing an IOP-reducing effect have been identified and studies are ongoing to assess and understand how these compounds can be developed into pharmaceutical agents.[30]

Small interference RNA has been shown to prevent certain genes (depending on its targets) from expressing specific proteins. An animal experiment revealed that small interference RNAs against adrenergic receptors, acetylcholinesterase, and ATPases administered intravitreally can reduce IOP, which started to work after the third dose and having maximal effect at days 3–5. Intravitreal injection involving only small doses mean that systemic absorption is minimal, and hence systemic side effects are negligible. The downside is that the experimental route of administration is invasive. Studies are ongoing to devise a less invasive mode of administration, because this treatment approach is showing promise in view of its prolonged effects on IOP-lowering.[30]

Gene Therapy in Glaucoma

Gene mapping to find the cause of glaucoma and OH is ongoing, with regular updates in the various journals. With the passage of time, more and more genes are discovered to be associated with OH and glaucoma. As these genes are identified, biochemical mechanisms underlying the disease are being recognized, and new methods of therapy can be developed for management of OH and glaucoma.[31]

Neuroprotection

Reduction of IOP is the still the most common method of preventing progressive glaucomatous optic neuropathy, but clinical experience suggests it is only partly effective. Because glaucoma is a progressive neurodegenerative disease of the retinal ganglion cells and axons, neuroprotection could be an additional therapy to prevent progressive optic neuropathy. Neuroprotection has been shown to be of benefit in other neurological conditions, such as Parkinson's disease, stroke, and Alzheimer's disease. Since glaucoma has in common with these conditions the mechanisms of neuronal injury of hypoxia, oxidative stress, and apoptosis, researchers have been prompted to consider whether neuroprotection may also have a potential role in the treatment of glaucoma.[32–34] In this context, a number of agents have been investigated, as follows.

Apoptosis inhibitors

Caspase-3 inhibition have been shown in animal glaucoma models to slow down the progression of retinal ganglion cell apoptosis. Furthermore, it has been shown that there are similarities in the mechanisms of molecular cell death between glaucoma and Alzheimer's disease, raising the possibility that neuroprotective strategies used in Alzheimer's disease may also have a role in treating human glaucoma.[35]

Tumor necrosis factor alpha is a mediator of cellular apoptosis causing mitochondrial cell death by both caspase-dependent and caspase-independent pathways. GLC756, a dopamine receptor antagonist acting as a tumor necrosis factor alpha inhibitor in mast cells in rat model,[36,37] is currently being investigated as a potential neuroprotectant.

Calpain in a calcium-dependent proteolytic enzyme which has been implicated in causing necrosis and apoptosis of ganglion cells. Several studies have shown the role of calpain in glaucoma[38] and hypoxic cell death.[39] SJA6017 (calpain inhibitors VI) and calpain 1 inhibitors protect retinal ganglion cells and are currently being studied for their role in OH and glaucoma.[40]

Neurotrophic factors

Neurotrophic factors, such as brain-derived neurotrophic factor, nerve growth factor, neurotrophins 3, 4 and 5, glial cell-derived neurotrophic factor, ciliary neurotrophic factor, and fibroblast growth factor-2, are some of the important neuromodulators and neurostimulants which are currently being studied for a potential role in the management of glaucoma and OH.[41] They selectively target TrkA[42] or TrkB[43] receptors in retinal ganglion cells and thus may offer protection to these cells.

Calcium channel blockers

Raised calcium is neurotoxic through activation of calcium-dependent catabolic enzymes. The exact mechanism of action of calcium channel blockers as neuroprotectants is unknown. The suggested to mechanisms of calcium channel blockers include direct action on calcium and improvement in ocular blood flow. Nifedipine, verapamil, and diltiazem have been shown to be effective in normal tension glaucoma[44,45] and nilvadipine in open angle glaucoma.[46] Other calcium channel blockers, such as flunarizine and lomerizine, have shown to be effective in animal models but not in humans.[47] Calcium channel blockers should be used with caution because of their systemic hypotensive effect which may be potentially detrimental to optic nerve head perfusion.[48]

Free radical scavengers and antioxidants

Several free radical scavengers are currently being studied for their role as neuroprotectants. Coenzyme Q10 have yet been studied as a neuroprotectant in animals. No human trials have yet been conducted to date.[49–51] Several mechanisms of action have been proposed, such as an action on the mitochondrial transport chain, thereby producing energy to overcome the effect of excessive glutamate, inhibition of inflammatory and autoimmune factors, such as NF-κB, and also acting as a free radical scavenger. Coenzyme Q10 prevents oxidative damage to cells and thus protects retinal ganglion cells.

Vitamin E (alpha tocopherol) is a lipid-soluble vitamin which acts as an antioxidant in cells. Small studies have shown a protective effect in retinal cells by direct vasoregulatory and protein kinase C-mediated glutamate transport activity.[52,53] These results are very much in the initial stages and no concrete data are available.

Melatonin

Melatonin is a neurohormone produced by the pineal gland and is a regulator of circadian rhythm. Its concentration in aqueous humor fluctuates and is highest at night time. Several studies have correlated diurnal changes in IOP with fluctuation in melatonin levels, and suggested that a melatoninergic mechanism is involved in the circadian rhythm of IOP. Oral administration of melatonin has been shown to reduce IOP in humans, and topical administration of melatonin has shown a similar IOP-lowering effect in animal models, with the effect lasting as long as nine hours in rabbits and 18 hours in monkeys. The mechanisms of action of melatonin and its analogs are not clearly elucidated to date, but studies are ongoing to produce a clearer idea of its mechanisms of action and how best to harness it as a pharmaceutical agent to reduce IOP in OH and glaucoma.[30]

Ginkgo biloba

Ginkgo biloba (EGb 761) is a platelet-activating factor which acts as an antioxidant, free radical scavenger, glutamate NMDA receptor inhibitor and nitric oxide inhibitor to increase the survival of retinal ganglion cells.[54,55] It should be avoided in patient already on some antiplatelet agent such as aspirin to decrease the risk of bleeding. Although evidence to support its use is very limited[56,57] some ophthalmologists employ it in the treatment of cases of advanced glaucoma.

Nitric oxide synthase inhibitor

Nitric oxide synthase 2 is present in astrocytes in optic nerve heads from glaucomatous human eyes, but not in normal eyes. It has been postulated that nitric oxide synthase 2 is one of the key players in inducing apoptosis of retinal ganglion cells in glaucoma. Aminoguanidine inhibition of nitric oxide synthase 2 has been shown to delay retinal ganglion cell loss in animal glaucoma model, without any effect on IOP. Aminoguanidine was administered in the animals' drinking water. There were no significant systemic side effects reported.[58]

NMDA receptor antagonists

Memantine (1-amino-3,5-dimethyladamantane) is an NMDA glutamate receptor antagonist approved as a neuroprotectant in Alzheimer's dementia. It has been shown to reduce functional loss of vision associated with monkey experimental glaucoma safely and effectively, although it has no IOP-lowering effects. This was achieved by orally administering memantine to the monkeys. There were no systemic adverse reactions noted.[59,60] Despite the promise of these early studies, a potential role for memantine remains uncertain. Two parallel double-blind trials have been conducted with memantine in humans using different doses. One of the studies showed slower rate of progression

of glaucoma with higher doses of memantine but the second study showed no significant difference in visual field progression between treated and placebo group. As a consequence, there was no basis for the approval of memantine for use in glaucoma.[61] Flupirtine, a tricyclic antidepressant, especially when combined with interferon-β act as a neuroprotectant in animal studies. No human trial has been done until now. No human trial has yet been carried out.

Riluzole[62] and dextromethorphan[63] are two other NMDA antagonists with neuroprotectant activity.

Immune mediators

Glatiramer acetate, an immune mediator, is a synthetic oligopeptide used in multiple sclerosis, have been shown to increase survival of retinal ganglion cells in animals. Geranylgeranylacetone, an acyclic polyisoprenoid, and amyloid beta antibody are two other immune mediators in which neuroprotectant activity has been demonstrated.

Ephrins

Ephrins act as axonal guidance molecules and their levels have been shown to rise in central nervous system injuries in adults (which also include nerve layer damage from raised IOP). They are seen both as inhibitors of regrowth of regenerating axons as well as stimulating astrocyte activation and gliosis. This means that the damaged axons do not degenerate, and in addition, glial scar formation acts as a seal to the site of injury to provide a physical barrier to neuronal degeneration. Therefore, it is postulated that the inhibition of ephrins may offer a new strategy in preventing effects of neurodegeneration in the retina secondary to raised IOP.[64–66]

Heat shock proteins

Heat shock proteins are groups of different proteins expressed as a reaction to cell stress. These proteins enhance survivability of cells exposed to what would otherwise be a lethal stress. Among the protein groups, only heat shock protein 27 can protect dorsal root ganglion neurons from apoptosis induced by nerve growth factor withdrawal. Therefore, heat shock protein 27 has been investigated to determine if it has a similar protective effect on retinal ganglion cells which are put under stress. Heat shock protein 27 applied to the retinal ganglion cells in animal glaucoma models resulted in increased resistance to apoptosis induced by ischemia-reperfusion injury. This forms a basis for further studies into its role in neuroprotection in eyes with raised IOP. Currently the need for invasive administration is a major obstacle. No adverse systemic reactions were reported.[67]

Glutamate

Release of glutamate has been implicated as a mechanism of retinal ganglion cell death/degeneration in glaucoma. It has been demonstrated that glutamate plays a pivotal role in the induction of apoptosis of retinal ganglion cells in retinal damage, caused among other things, raised IOP. Glutamate-modulating agents were administered intravitreally into eyes with experimentally raised IOP in an animal model, with a reduction in the apoptosis rate in retinal ganglion cells. There were no reports of adverse systemic reactions in this study. The modulation of glutamate release has thus been demonstrated to be a viable potential neuroprotective strategy in glaucoma-related animal models. The requirement for intravitreal drug delivery may again be considered a significant obstacle and more development is needed to make this an effective non-invasive drug strategy for future use.[68]

Sulfhydryl

Sulfhydryl is a naturally occurring organic sulfur molecule that can influence enzymatic activities in proteins of living beings. Activated, it can induce apoptosis. Therefore, tris(2-carboxyethyl) phosphine, a sulfhydryl reductant which does not contain oxidizable sulfhydryls, injected intravitreally has been shown in animal models to confer a neuroprotective effect for retinal ganglion cells. No toxic effect of retinal ganglion cell survival was observed, and no syssystemic side effects were noted. Once again, the need for invasive administration presents a significant difficulty and more studies are required to improve our understanding of the underlying mechanism of action of this approach and to devise a less invasive method of effectively administering this agent.[69]

Lastly, patient compliance is of paramount importance to ensure sustained control of IOP. Poor compliance can be partly due to the discomfort in using the medications. Newer, less irritable IOP lowering agents are being developed for better patient comfort, as this will increase compliance among patients.

Summary

A small summary can be drawn from the research into neuroprotection as a different approach in managing OH and glaucoma, in that it utilizes the idea of inhibiting the many identified factors that promote apoptosis of retinal ganglion cells to preserve functional vision, with or without consideration of IOP-lowering. Although this approach is laudable, more studies are needed to look for new modifiable factors that can trigger retinal ganglion cell apoptosis under conditions of raised IOP. This will then allow for a more concerted effort in targeting and inhibiting major factors contributing to the apoptotic process in OH and glaucoma. In conclusion, the search continues for improved treatments for ocular hypertension and glaucoma. We can be optimistic that some of the agents currently under investigation may progress successfully through clinical trials to provide the clinician with safer and more effective weapons in the fight against glaucoma-induced blindness.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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