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Glaucoma 2.0: Neuroprotection, Neuroregeneration, Neuroenhancement

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Abstract

Glaucoma is a progressive neurodegenerative disease of retinal ganglion cells (RGCs) associated with characteristic axon degeneration in the optic nerve. Clinically, our only method of slowing glaucomatous loss of vision is to reduce intraocular pressure (IOP), but lowering IOP is only partially effective, and doesn't address RGCs' underlying susceptibility to degeneration. Here we review recent steps forward in our understanding of the pathophysiology of glaucoma, and discuss how this understanding has given us a next generation of therapeutic targets by which to maintain RGC survival, protect or rebuild RGC connections in the retina and the brain, and enhance RGC function.

INTRODUCTION

Glaucoma is the most common cause of irreversible blindness worldwide, and the most common optic neuropathy[4]. It is essentially a collection of neurodegenerative diseases that result in retinal ganglion cells (RGC) axon degeneration and death. Glaucoma is associated with a typical appearance of structural damage at the optic nerve head, with neuroretinal rim thinning, excavation (cupping), and sectoral retinal nerve fiber layer defects.[3] Glaucoma also affects the retinal and central visual pathways, leading to degenerative changes upstream in the retina and downstream in the lateral geniculate nucleus and visual cortex.[3] Glaucomas are often categorized by anterior chamber anatomy (open- and closed-angle) and whether they are primary or secondary. Among the primary open angle glaucomas (POAG), clinicians and researchers often further classify patients who start with intraocular pressures (IOP) in the normal range as low- or normal-tension glaucoma (NTG), although the distinction between POAG and NTG may not ultimately be clinically meaningful, as patients with glaucomatous damage starting at high or low IOP may both benefit from IOP-reducing therapies. This leaves a series of fundamental questions for clinicians and scientists to consider: why are certain people's RGCs more or less susceptible to IOP, and how can we target these patients to reduce this susceptibility? We know almost nothing about the first question, and a considerable investment in genetics studies and molecular investigations may yet yield some progress. Even without knowing why some patients' RGCs are so vulnerable to IOP, however, here we discuss the considerable progress made on reducing this susceptibility and thereby deriving new approaches to treating glaucoma.

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COMPLIMENTING IOP-LOWERING THERAPY

Although IOP is no longer part of the definition of glaucoma, it is the only modifiable factor proven to decrease both the risk of disease onset and its progression. A series of randomized clinical trials have demonstrated that lowering IOP protects against glaucomatous optic nerve and visual field loss in patients with advanced glaucoma, newly diagnosed glaucoma, high IOP but no glaucoma, and glaucoma starting with lower IOP (NTG) (Table 1). Of particular note, the collaborative normal tension glaucoma study (CNTGS), the ocular hypertension treatment study (OHTS) and the early manifest glaucoma trial (EMGT) all yielded excellent evidence of the effect of IOP lowering on preserving visual function, whether by topical therapy, laser trabeculoplasty, or surgical trabeculectomy.

On the other hand, these studies also revealed that despite IOP lowering, some patients showed progressive glaucomatous disc changes and/or visual field loss. It is probable that with even more aggressive IOP lowering, progression could have been reduced even further. Nevertheless, the challenges to IOP-lowering therapy as the sole approach to glaucoma are well-documented: patients have difficulty tolerating or complying with multi-drop therapy, surgical success rates are still not satisfying, and some patients progress despite reaching their lowest achievable IOP. Thus, attention must turn to RGCs and the mechanisms of susceptibility and degeneration in the retina, optic nerve and brain to generate new approaches to glaucoma treatment.

COMPLEMENTING IOP-LOWERING THERAPY

Understanding the pathophysiology of glaucoma

As IOP-lowering treatments alone are inadequate, what can be done to target RGC susceptibility and degeneration? Our understanding the basic pathophysiology of glaucoma comes both from clinical observation and more recently from animal models. Significant risk factors for glaucoma include elevated intraocular pressure, age, race, and family history. A role for family history as a risk factor and potential insight into the molecular pathophysiology of glaucoma is further supported by our understanding of the genetics of the disease, through identification of genetic loci and causative genes for various forms of glaucoma.[5] Genes have been associated with adult-onset POAG (*MYOC, WDR36, OPTN, NTF4*), congenital glaucoma (*LTBP2, CYP1B1*), pseudoexoliative glaucoma (*LOXL1*), and normal tension glaucoma (*OPTN*), although most POAG patients may not have any of these gene mutations or polymorphisms. For example, optic atrophy 1 (*OPA1*), the cause of dominant optic atrophy and also mutated in some congenital optic nerve hypoplasias, has been associated with NTG in Japanese and Caucasian populations, but not with POAG cases with elevated IOP in Caucasian, African-American, and West African populations.[6] Familial glaucomas are relatively rare, however, and only a few genes have thus far been validated as risk factors for glaucoma. Broader genome-wide association studies may still yield more genes to consider, but unfortunately little biological insight into RGC susceptibility to glaucomatous damage has yet been derived from the identification of these human glaucoma-associated genes. Certainly more effort will lead to more understanding.

The progression of human disease also makes it clear that initiation or propagation of glaucomatous damage must be localized at or around the optic nerve head (see references in [3]). First, focal areas of optic nerve cupping correlate with focal areas of RGC loss and decreased peripheral vision. Second, typical glaucomatous arcuate scotomas do not spread across the horizontal midline in the nasal visual field, even though RGC cell bodies might be immediately adjacent to each other there, suggesting the spread of dysfunction does not propagate in the retina. Rather, the progression spreads according to the distribution of the RGC axons entering the optic nerve. Third, replicating IOP-induced RGC axon and cell

body loss in pre-clinical animal glaucoma models supports the importance of the optic nerve head. Whether the pathophysiology is primarily axonal, glial, or vascular, and more particularly at the level of the prepapillary, prelaminar, laminar or immediately postlaminar optic nerve, remain unanswered questions.

How do RGCs Die in Glaucoma? Initiating Mechanisms

A number of mechanisms have been invoked to explain RGC pathology in glaucoma, including chronic intermittent ischemia, reactive oxygen species, excitoxicity, defective axon transport, trophic factor withdrawal, and loss of electrical activity (see references in [3]). Vasospasm, defective vascular autoregulation, or mechanical compression of the microvasculature at the lamina cribrosa may affect perfusion of the optic nerve head, which in turn may cause RGC ischemia. Both acute and chronic ischemia contribute to oxidative stress, brought on by an unbalanced metabolic demand and associated with production of free radicals or reactive oxygen species (ROS). Increased ROS and decreased concentrations of antioxidants have been found in the glaucomatous vitreous, as has oxidative DNA damage and oxidative alterations of the trabecular meshwork. Calcium-channel blockers (CCBs) have antivasospastic and presumably thereby anti-ischemic effects, and thus have been studied as potential neuroprotectants in animal models.[7] It is unclear whether the activity of CCBs is mediated through direct action on calcium or indirectly through improved optic nerve blood flow, but any benefit from CCBs must be weighed against the potential risk of systemic hypotension, which may result in a reduction of optic nerve head perfusion pressure.[8]

Excitotoxicity is thought to occur when dying cells release excessive amounts of neurotransmitters such as glutamate. Hyperactivation of N-methyl-D-aspartate (NMDA) - sensitive glutamate channels in adjacent may lead to a deleterious increase in intracellular calcium, activation of nitric oxide synthase resulting in nitric oxide production, and other metabolic dysregulation, injuring these adjacent RGCs in a secondary or bystander cell death. A possible confounding issue is whether RGCs are themselves directly injured by excessive glutamate, or the cells around them such as amacrine cells or Muller glia bear the brunt of that insult, and then their loss leads to RGC death as a secondary effect, as suggested by experiments performed on RGCs purified and cultured in vitro.[9] Whether glutamate is directly or indirectly toxic to RGCs, blocking excessive glutamate activation remains an area for investigation. For example, aminoguanidine is a potent inhibitor of such excitotoxicity and has been studied as a neuroprotective agent, but results are inconclusive.[10, 11] Clinical results from other neurodegenerations or stroke have been mixed as well, with few drugs demonstrating clear clinical benefit. For example, riluzole is a drug approved for amyotrophic lateral sclerosis that delays the need for tracheostomy or ventilator-dependence, but its effect may not work through anti-glutamatergic effects. The anti-glutamate drug Memantine is approved for Alzheimer's disease; its application in glaucoma is discussed further below.

Defective axon transport was first demonstrated in animal models in response to experimentally elevated IOP over 30 years ago (see refs in [3]). Either through mechanically deforming the optic nerve head at the lamina cribrosa, or perhaps secondarily through ischemic or other mechanisms, elevated IOP leads to a blockade of the normal shuttling of cytoplasmic cargoes up and down the axon. RGCs depend on neurotrophic survival and growth signals from the retina, optic nerve, and their targets in the brain for survival. Glaucomatous blockage stops retrograde transport of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and likely of other neurotrophic factors (discussed below), all of which promote RGC survival and growth. RGCs may also become less responsive to trophic factors after injury, possibly as a result of decreased electrical activity

after optic nerve injury.[1] To what degree this contributes to RGC dysfunction or death in human glaucoma remains unknown.

Any of these insults may lead to dysregulation of other cellular processes. For example, accumulation of hyperphosphorylated tau and other abnormal proteins has been described in glaucoma patient retinas.[12] Abnormally folded proteins leads to endoplasmic reticulum (ER) stress and RGC apoptosis. ER stress is detectable in the retinal ganglion cell layer after IOP elevation or intravitreal NMDA injection.[13] Further investigation into ER stress may address whether it is an approachable target for glaucoma therapy.

How do RGCs Die in Glaucoma? Downstream Mechanisms

Even without knowing the underlying molecular or cellular mechanism by which RGCs are initially damaged in glaucoma, considerable progress has been made in understanding the downstream pathways that lead to RGC dysfunction and death. Ultimately, no matter the inciting pathophysiology, RGCs primarily die in glaucoma by apoptosis.[1] Apoptosis is the process of programmed cell death resulting in sequential degradation of intracellular organelles with ultimate final clean-up by phagocytic cells.

Apoptosis can be initiated by “extrinsic pathway” triggers including TNF-alpha, Fas ligand and TNF-related apoptosis-inducing ligand, or by “intrinsic pathways” that are activated after the loss of pro-survival signals from neighboring cells in the retina, optic nerve or brain.[2] Downstream of extrinsic and intrinsic pathway apoptosis initiators, these insults often involve mitochondrial-mediated signaling pathways. Activation of intracellular calcium-activated proteins like calcineurin and calpain and proteases called caspases, increased expression of pro-apoptotic genes such as Bax/Bid, and downregulation of anti-apoptotic genes such as Bcl-2/Bcl-xl lead to programmed cell death.[2] Thus, a fair amount is known about final common pathways leading to RGC death, even though the inciting insult in glaucoma is not yet defined. A better understanding of these interactions in specific pathologies may help speed the development of new specific anti-apoptotic therapies (discussed further below).

Furthermore, a number of these pathways are common to RGC death in other optic neuropathies. Many disorders insult RGC axons in the optic nerve, including ischemic, compressive or traumatic optic neuropathies, disc drusen, optic neuritis, papilledema, and others. Following any optic nerve axon injury, RGCs become dysfunctional and typically die. Loss of nerve fiber layer axons, optic atrophy, and vision loss are common clinical presentations, although there are specific clinical features that typically distinguish glaucoma including nerve head cupping, lack of pallor, and the pattern of visual field scotomas and preservation of central acuity until late in the disease. Nevertheless, these other optic neuropathies may share many of the same pathways of RGC degeneration, even if the inciting insults are fundamentally different, and animal models of other optic neuropathies are also contributing to our ability to address the critical question, How can we better prevent or reverse vision loss in glaucoma?

NEUROPROTECTION

Neuroprotection, the therapeutic paradigm designed to slow or prevent the death of neurons to maintain physiological function, has been a longstanding goal of clinical and basic neuroscience, to treat neurodegeneration in the eye, the brain, or the rest of the nervous system. Research into neuroprotection for glaucoma has taken advantage not only of pre-clinical glaucoma models, but also of models of other optic neuropathies. A number of neuroprotective strategies and drugs derived from the proposed pathophysiologies discussed above have passed through various stages of pre-clinical and clinical testing.

Memantine

For example, blocking glutamate excitotoxicity has been one of the most discussed approaches. Memantine, an NMDA glutamate receptor antagonist, was the first drug approved for use as a neuroprotective agent in moderate to severe Alzheimer's dementia. Evidence of its usefulness in glaucoma arose from animal glaucoma models, where it was shown that memantine is protective against retinal ganglion cell loss.[14] Data from a complex and expensive clinical trial in human glaucoma that did not meet its primary efficacy endpoint has still not been reported on by Allergan.

Brimonidine

Activating alpha-2 adrenoreceptors has also been plagued by conflicting data. Alpha2-adrenergic activation was first shown to be neuroprotective in animal models of focal cerebral ischemia.[15] Subsequent studies demonstrated the presence of alpha2- adrenergic receptors in the human retina.[16] Systemic administration of the alpha2 agonist brimonidine, FDA-approved for IOP lowering for glaucoma, protected RGCs in ocular hypertensive rat models.[17] Potential mechanisms for these neuroprotective effects include upregulation of brain-derived neurotrophic factor in RGCs and the retina, activation of cell-survival signaling pathways and anti-apoptotic genes, inhibition of ischemia-induced glutamate release, and modulation of NMDA receptor function.

Can brimonidine's potential for neuroprotection be realistically studied independent of its effect on IOP in glaucoma? In the recently reported Low Tension Glaucoma Treatment Study (LoGTS), patients randomized to monotherapy with brimonidine demonstrated less visual field progression than patients randomized to timolol, despite similar IOP lowering effect.[18] These data suggest that in addition to preventing visual field progression by lowing IOP, brimonidine also acted as a neuroprotective agent, although other explanations have been offered, for example if there are mild toxicities of timolol. Novel delivery systems for alpha2 agonists are currently in development and testing; alternative delivery might be capitalized on to improve on neuroprotective activity, for example in a trial using a surgical implant (clinicaltrials.gov identifier NCT00693485).

Other approaches

Other new pharmacologic approaches to neuroprotection are also in development for glaucoma or other optic neuropathies, for which clinical testing may precede glaucoma to minimize testing time (discussed further below). For example, caspase inhibition increases retinal cell survival in many models including glutamate excitotoxicity, and an siRNA-based caspase inhibitor is now in human testing in a multicenter trial for non-arteritic ischemic optic neuropathy (QPI-1007; clinicaltrials.gov identifier NCT01064505). Inhibiting nitric oxide synthases, and immunization with certain synthetic polypeptides to modulate immune function, may also prove valuable, although to date these strategies have not reached randomized controlled clinical trials in human patients with glaucoma. Traditional neurotrophic factors are strongly neuroprotective and also promote axon regeneration and enhance RGC function, and are discussed below, and other peptides such as activity-dependent neuroprotective protein (ADNP) and activity-dependent neurotrophic factor (ADNF) increase survival and axonal growth in RGCs *in vitro*.[19] Currently, clinical trials are investigating intravenous and intranasal formulations of such peptides in Alzheimer's and other neurodegenerative diseases.

OPTIC NERVE AXON REGENERATION

Although enhancing RGC survival is a critical first step, for RGCs whose axons have already been injured in the optic nerve, merely preventing apoptosis will not enhance

regrowth of axons back to targets in the brain. Protecting RGCs from death may be sufficient in some diseases in which temporary survival through an acute insult is all that is needed—perhaps in acute angle closure glaucoma or ischemic optic neuropathy, for example. In longer-standing insults where axons are severed, ideal therapies should also encourage axon regeneration, to rebuild connections from the eye to the brain.

Blocking Inhibitory Signals and Enhancing Intrinsic Growth Ability

Axon regeneration is inhibited by the mature optic nerve environment, where glia release inhibitory molecules that actively signal RGC axons to stop growing. A number of these molecules have been identified and drugs developed to overcome their inhibitory influences. For example, antibodies to the oligodendrocyte-derived protein Nogo are in clinical trials for spinal cord injury (ATI355; clinicaltrials.gov NCT00406016) and could be tested for an ability to enhance optic nerve regeneration or visual cortical plasticity. The signaling pathways within RGC axons that mediate such stop signals could also be clinical targets For example, many glial-associated inhibitory signals converge on the proteins Rho and Rho-kinase (also called Rock) in RGC growth cones. One small molecule inhibitor of Rho, Cethrin, has been tested in a Phase IIa trial for spinal cord injury, and a number of Rock inhibitors are being examined for their IOPlowering effects, but could also prove useful for enhancing optic nerve regeneration.

Other approaches to modifying RGCs' intrinsic capacity for axon regeneration are also making pre-clinical progress. Transcription factors including Kruppel-like factors[20] may be targeted by gene therapy-based approaches. Blocking the expression of signaling molecules like phosphatase and tensin homolog (PTEN) and suppressor of cytokine signaling-3 (SOCS3) may release the pro-growth and pro-regeneration activities of mTOR and CNTF to greatly enhance long-distance optic nerve regeneration.[21, 22] Such data suggests that manipulation of intrinsic growth control pathways will provide a therapeutic approach to promote axon regeneration in optic neuropathies.

Neurotrophic factors

There are also molecules that could simultaneously enhance RGC survival and axon growth. For example, neurotrophins have been a very promising class of drugs for neurodegenerative diseases. A number of neurotrophins have been tested in human clinical trials, including BDNF for amyotrophic lateral sclerosis (ALS), CNTF for ALS and for macular degeneration, GDNF for Parkinson's disease, and NGF for Alzheimer disease, although despite this promise, none have yet succeeded in humans, in part because of complications associated with having to deliver them to the brain. Specific delivery to the eye may avoid such complications, and all four of these have shown promise for neuroprotection and regeneration of RGCs in pre-clinical glaucoma models,[23] although a temporary increase in RGC survival after optic nerve injury may not be sustained, and overexpression of trophic factors using viral vectors does not solve this problem, possibly because of downregulation of trophic responsiveness.[24] Stimulating RGCs with electrical activity, or pharmacologically elevating one of electrical activity's downstream mediators cyclic adenosine monophosphate (cAMP), greatly potentiates the pro-survival and growth effects of neurotrophic factor treatment, and may prove critical to neurotrophic factor efficacy.[1]

Nevertheless, there is considerable excitement surrounding neurotrophic factors that are approaching clinical trials in human glaucoma. For one, CNTF-expressing cell lines were encapsulated into a semi-permeable membrane that allows the CNTF to diffuse out but should prevent the immune system from attacking the cells themselves. Made by Neurotech, this CNTF-secreting device (NT-501) gets surgically implanted just inside the pars plana where it may reside indefinitely. This device has been through phase II trials in humans for

retinitis pigmentosa and macular degeneration without serious adverse events,[25] and entered phase I clinical trials for POAG in 2011 (clinicaltrials.gov NCT01408472).

NGF is a second neurotrophic factor under study for glaucoma. With demonstrated efficacy in a number of pre-clinical models, a first-in-human trial of 3 patients treated with a topical NGF formulation was recently reported.[26] Although it is impossible to draw any conclusions about efficacy from this report, it motivates the design of a proper, placebo-controlled randomized clinical trial. In addition, small molecule analogues of NGF have also been developed and shown to be effective in protecting RGCs in a pre-clinical model,[27] and one of these is in clinical trials for dry eye (Mim-D3; clinicaltrials.gov NCT01257607) and could thereafter be studied for glaucoma.

Other approaches

A surgical approach to enhancing RGCs' regenerative capacity with a simple lens injury could be investigated now. Breaching the lens capsule with a single needle poke induces a low grade inflammatory response thought to be pro-survival and progrowth. [28] A number of issues would have to be considered to try this in humans, including the rapid formation of a cataract, whether to give steroids that might inhibit a positive inflammatory response, and the relatively short-term nature of the effect, at least compared to the long-term horizon of most chronic glaucomas. Pursuing the molecular basis for the effect, which may be due to any of a number of proteins including crystallins released from the lens, CNTF, or oncomodulin, may prove more realistic for translation to human use for glaucoma.

Finally, stem cells hold great promise for neurodegenerative diseases like glaucoma. Although coaxing stem cells to turn into RGCs and connect from the eye to the brain may take considerably more work, in the short term, stem cells may serve as little neuroprotection and regeneration workhorses, pumping out survival and growth factors to address the RGCs that are still alive in glaucoma. Stem cells injected intravitreally have been shown to enhance retinal ganglion cell axon survival and presumably cell body survival in a pre-clinical model of glaucoma.[29] Hopefully, properly designed clinical trials will not get derailed by medical tourism, which continues to attract desperate patients to unregulated clinics abroad.

NEUROENHANCEMENT

In the Alzheimers disease literature, neuroenhancement refers to short-term improvements in cognitive or emotional function derived from specific treatments. Both anti-dementia acetylcholinesterase inhibitors and memantine may work through acute neuroenhancement. Similarly, drugs that improve RGC function might acutely increase vision in glaucoma. Rather than simply "neuroprotect" the remaining RGCs from dying over the long term, such treatments might "neuroenhance" RGC function in the short term.

Is there a window between dysfunction and death in which we could intervene to enhance RGC function and boost patients' vision? Before RGC axons are severed in the optic nerve or fully die in the retina, they may be merely dysfunctional. RGC dysfunction versus death cannot be distinguished by current visual field testing or optic nerve structural measurement. A number of indications, however, suggest that there is a window between dysfunction and death in glaucoma.

First, electrophysiological measurement of RGC function using pattern electroretinogram (pERG) demonstrates reversible dysfunction after acute pressure lowering in glaucoma patients. Steady-state pERG optimized for glaucoma screening is a noninvasive, objective method of measuring RGC function and has high test-retest repeatability.[30] The pERG

stimulus isolates the RGC response using a reversing grating pattern that carries no change in space-averaged luminance over time, but is particularly good at stimulating RGC action potentials with high-contrast edges. The RGC pERG signal is reduced in glaucoma patients compared with age-matched controls,[30] and correlates with central visual field sensitivity values as well as optic nerve and retinal nerve fiber layer anatomic measures,[31] although the dynamic range of pERG is relatively small and may be limited with current technology to early glaucoma. pERG abnormalities may also precede visual field changes in early glaucoma and ocular hypertensive subjects.[32] Importantly, pERG may be capable of measuring reversal of RGC dysfunction in glaucomatous eyes that undergo pharmacologic reduction in IOP in the clinic[33] and after trabeculectomy.[34]

Second, small improvements in visual field performance have been reported after acute IOP lowering in glaucoma patients. For example, one study with 54 patients randomized to three topical therapies showed a concomitant reduction of IOP (7.8 mm Hg) and improvement in mean deviation on visual field testing (0.84 dB) at 4 weeks.[35] Of course, such studies using automated perimetry are easily confounded by biases including regression to the mean and practice effects, making interpretation difficult.

Third, animal models clearly demonstrate that RGC death occurs only very late in the disease.[3] When rodents are subjected to acute elevations of intraocular pressure, axon transport slows first, frank axon severing is observed second, and RGC death occurs only relatively late. Thus, in both animals and humans, a window between dysfunction and death may provide a window for neuroenhancement therapies to take effect.

What treatments could prove neuroenhancing? Any treatment that acutely improves RGC health and function may be considered a neuroenhancement drug, possibly including IOP-lowering treatments as discussed above. Neurotrophic factors, for example, hold great promise for neuroenhancement, as they typically improve RGC health and may specifically act at the synaptic level to enhance function.

Other drugs have been studied in glaucoma that may have neuroenhancing effects. For example, cytidine-5'-diphosphocholine (citicoline or CDP-choline), an intermediate in the biosynthesis of the membrane lipid phosphatidylcholine, is available by prescription in Europe and as an over-the-counter supplement in the US marketed for stroke, Alzheimers disease, and other neurodegenerations. Although its mechanism of action remains unclear, a series of clinical trials including one randomized controlled trial have demonstrated improvement on visual field testing, VEP and pERG in glaucoma patients.[36, 37]

Electrical activity may prove neuroprotective and neuroenhancing for RGCs in glaucoma (see refs in [1, 24]). RGCs die if electrical activity is blocked with tetrodotoxin, whereas their survival is enhanced by electrical activity *in vitro* and *in vivo*. In a preclinical model, transcorneal electrical stimulation with a contact lens electrode promoted RGC survival one week after optic nerve injury. Transcorneal or transorbital electrical stimulation with either contact lens or periorbital skin electrodes can stimulate RGCs in humans to yield visual phenomena such as phosphenes, and have entered early clinical use for optic neuropathies including glaucoma. In one published case report, transorbital electrical stimulation over the course of 10 days gave a suggestion of acutely enhanced visual function,[38] which may act through local RGC enhancement or by stimulating brain plasticity. Together these data have motivated further human trials in optic neuropathies and stroke (e.g. clinicaltrials.gov identifiers NCT01270126, NCT01280877 and others).

In addition to the promise of acutely enhancing patients' functional vision, another motivation to consider a search for neuroenhancing therapies concerns technical issues surrounding glaucoma clinical trials. In a slowly progressing, chronic disease like POAG/

NTG, demonstrating neuroprotection requires long trials and/or larger numbers of patients. This is in contrast to the short trials required for testing IOPlowering drugs, for example, and likely explains why pharmaceutical companies have focused primarily on bringing IOP drugs to market.

Detection of progressive glaucomatous injury and the definition of study endpoints continue to be problematic, particularly as the FDA still has yet to approve a glaucoma endpoint other than IOP reduction or visual field testing.[39] Histologically, half of the RGCs may already be lost even before the onset of visual field damage[3] suggesting that the evaluation of function should be complemented with the evaluation of structure. However, even adding structural measures of RGC axons and the optic nerve head using stereo photography, confocal scanning laser tomography, scanning laser polarimetry, and optical coherence tomography[40] may not address the length of time needed to show preservation of RGCs.

Thus it may take many years to statistically confirm neuroprotection in a new drug trial, and coaxing RGC axons to regenerate all the way down the optic nerve to reconnect with their targets in the brain may take even longer. Demonstrating neuroenhancement, that is to say, an acute improvement in RGC structure or function, may be possible on a considerably shorter time scale, and this should greatly encourage moving potential new classes of glaucoma therapies into clinical testing.

DISCUSSION

In summary, while IOP-lowering will remain a mainstay of glaucoma therapy, and is certainly a very successful “neuroprotectant” in itself, the motivation for complementary approaches to glaucoma therapy is higher than ever. Such novel therapies may (1) provide IOP-independent treatments for glaucoma compatible with or even overcoming the need for IOP lowering; (2) enhance RGC function in the short term, improving patients’ vision; and (3) point towards shorter paths to clinical testing and ultimately thereby augment patients’ access to new therapies.

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TABLE 1

Randomized controlled trials demonstrating protection against visual field loss by lowering IOP. Note that AGIS data in support of this effect is derived from post-hoc associative analyses, and CIGTS data demonstrates similarity of medical and surgical IOP-lowering approaches to visual function outcomes.

Study	OHTS	CNTGS	EMGT	AGIS	CIGTS
# patients	1636	230	255	738	607
Randomization	RCT	RCT	RCT	RCT	Longitudinal RCT
Group 1	Topical therapy	Medical or surgical	ALT and betaxolol	ALT–trabeculectomy–trabeculectomy	Filtration surgery
Group 2	Obs	Obs	Obs	trabeculectomy–ALT–trabeculectomy	stepped medication treatment regimen
IOP lowering goal (%)	20%	30%	25%	Three groups: 1. IOP <18 mm Hg 100% 2. <18mmHg 75–100% 3. <18mmHg 50–75% 4. <18 mmHg <50%	3 groups: maximum, mean, standard deviation (SD), range, proportion less than 16, 18, 20, or 22 mmHg
Follow-up	72 months (median)	4,7 years (untreated-treated, respectively)	5 years	6 years	3–9 years
Progression in Group 1	4.4%	12%	45%	Greater worsening of visual field defect score for each of the three elevated IOP groups than for the reference group 1	34.1%
Progression in Group 2	9.5%	35%	62%	The average IOP in group 1 was 12.3 mm Hg over 6 years, and their mean change from baseline in visual field defect score ranged from −0.26 (improvement) at 2 years to +0.46 (worsening) at 4 years	23.1%
Reference	Arch Ophthalmol 120:714–20	Am J Ophthalmol 126:487–97	Ophthalmology 114:1965–72	Am J Ophthalmol 130:429–40	Ophthalmology 118:1766–73

Obs, observation; IOP, intraocular pressure.