YALE JOURNAL OF BIOLOGY AND MEDICINE 89 (2016), pp.73-79.

REVIEW

YJBM

Neurodegeneration and Neuroprotection in Glaucoma

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Glaucoma is the principal cause of irreversible blindness in the world. The disease leads to progressive optic nerve degeneration with a gradual loss of retinal ganglion cells. Neurodegeneration in glaucoma extends beyond the eye into the lateral geniculate nucleus and visual cortex, and the disease even shares some characteristics with other central nervous system degenerative disorders. Glaucoma destroys neurons through oxidative stress, impairment in axonal transport, neuroinflammation, and excitotoxicity. Autophagy may promote or inhibit disease progression. Currently, lowering intraocular pressure is the only way proven to delay glaucoma advancement. However, many new therapies are being developed, including antioxidants, adenosine receptor antagonists, Rho-pathway inhibitors, stem cell therapy, and neurotrophic factors. These therapies focus on neuroprotection, and they may eventually halt glaucoma progression or reverse the process of the disease itself.

INTRODUCTION

Glaucoma is a group of diseases with progressive loss of the neuroretinal rim at the optic nerve that causes a characteristic degenerative optic neuropathy. About 3.5 percent of the world population ages 40 to 80 has glaucoma [1]. In fact, glaucoma is one of the leading causes of blindness in the world, second only to cataracts [2].

Patients with mild to moderate glaucoma are often asymptomatic. They may experience gradual loss of peripheral and/or central vision as the disease advances. With the exception of acute angle closure glaucoma, glaucoma can often be hard to notice until damage has already occurred. For this reason, people are encouraged to get routine eye exams, especially if they have any of the known glaucoma risk factors, such as a positive family history; Black, Hispanic, or Asian ancestry; a history of ocular trauma and myopia; diabetes; hypertension; or long-term corticosteroid use. Suspicion for glaucoma is increased in patients with high intraocular pressure (IOP), visual field defects, and an enlarged cup-to-disk ratio of the optic nerve. Larger cup-to-disk ratio can be a result of optic nerve neuroretinal rim thinning secondary to destruction of retinal ganglion cell (RGC) axons, vasculature, and glia [3]. Fundoscopic exams may also reveal hemorrhages on the optic nerve disc in glaucoma patients [4].

Glaucoma has traditionally been considered a disease of the eye, but recent research has linked it to degeneration of the central nervous system (CNS). Glaucoma-associated neurodegeneration has been noted in the intracranial optic nerves, lateral geniculate nucleus (LGN), and visual cortex of primates and humans [5-7].

One case study compared the brain of a glaucoma patient with a superior visual field defect to three brains of age-matched controls without neurological or ocular disease [7]. Tissue samples from the LGN at autopsy showed shrunken neurons with smaller nuclei and more globoid cytoplasm in both the magnocellular and parvocellular layers in the glaucoma patient compared to the controls. In addition, cortical ribbon thickness under the calcarine sulcus was diminished, and optic nerve tissue was heavily atrophied. Another study demonstrated decreased cell density in the magnocellular layer in glaucoma patients compared to healthy controls [8]. These studies indicate that the effects of glaucoma can extend

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†Abbreviations: IOP, intraocular pressure; RGC, retinal ganglion cell; CNS, central nervous system; LGN, lateral geniculate nucleus; POAG, primary open angle glaucoma; TM, trabecular meshwork; NTG, normal-tension glaucoma; BDNF, brain-derived neurotrophic factor; TNF-α, tumor necrosis factor-alpha; NMDA, N-Methyl-D-aspartate; AD, Alzheimer's disease; PD, Parkinson's disease; ACh, acetylcholine; ROCK, Rho-associated coiled-coil containing protein kinase

Keywords: glaucoma; neurodegenerative diseases; intraocular pressure; stem cells; neuroprotection

beyond the eye into areas that process visual information within the brain.

Although glaucoma is predicted to affect more patients as the world population grows and the average lifespan increases [1], the mechanism of the development and progression of this neurodegenerative disease is still largely unknown. Currently, IOP is the only modifiable risk factor for glaucoma and essentially the center of treatment. However, with recent increased understanding of the neurodegenerative process in glaucoma, neuroprotective treatment has been proposed as a different approach to improve our management of this condition.

MECHANISMS OF GLAUCOMATOUS NEURODEGENERATION

Primary open angle glaucoma and the MYOC gene

Primary open angle glaucoma (POAG) is the most-common subtype of glaucoma. This multifactorial disease is usually chronic, slowly progressive, and characterized by decreased aqueous humor outflow and subsequent optic nerve damage without any identifiable etiology. Risk of POAG increases with advanced age, African-American race, myopia, low diastolic perfusion pressures, and thinner corneas [3,9]. In contrast to most other types of glaucoma, POAG can occur with either elevated or normal IOP.

The cause of POAG can be directly linked to genetics in a small proportion of patients. Mutations in the *MYOC* gene account for about 4 percent of adult-onset and 10 percent of juvenile-onset POAG [10,11]. The *MYOC* gene codes for myocilin, a protein with an unknown function made by the ciliary body and trabecular meshwork (TM) [12,13]. Patients with the *MYOC* mutation secrete less myocilin, which instead accumulates in the cells of the TM. This poisons the TM cells, destroying the outflow pathway for aqueous humor, leading to higher IOP and optic nerve damage [14].

Normal-tension glaucoma and optic nerve ischemia

POAG that occurs with a normal IOP (10-21 mmHg) is called normal-tension glaucoma (NTG), or low-pressure glaucoma, which happens in about 50 percent of undiagnosed glaucoma cases [15]. The cause of optic nerve damage is still unclear in patients with NTG as their IOPs are never observed being elevated. Patients with NTG are more likely to have had an episode of major shock or chronic low blood pressure than those with elevated IOP [16]. This suggests that optic nerve ischemia may contribute to NTG development. A cohort study indicated that silent cerebral infarct is associated with a higher risk of NTG visual field progression [17]. Patients with NTG may have a lower probability of developing blindness in their affected eye compared to those with increased IOP, possibly due to a slower disease progression rate [18,19]. Even though the pathophysiology of NTG is not fully understood, lowering IOP still has beneficial effects and remains the primary treatment strategy in these patients [20].

Oxidative stress, axonal transport impairment, and neuroinflammation

In addition to possible chronic nerve ischemia related to hypovolemia, optic nerve damage can be mediated by many other factors. Increased IOP may compress the blood supply to the nerve [21-23]. As the nerve becomes more hypoxic, mitochondria are damaged, leading to reactive oxygen species formation and cellular stress [24]. Furthermore, a high IOP impedes axonal transport, preventing the RGCs from receiving essential neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [25,26]. The excess pressure also stimulates microglial cells in the optic nerve head to release pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), which are toxic to RGC axons [27]. Microglia also release C1q, a protein that starts the complement cascade, which is increased in glaucoma [28]. In fact, minocycline- or chemokine receptor CX3CR1-induced suppression of microglia increased survival of RGCs, further implicating these immune cells in the pathogenesis of glaucoma [29].

Excitotoxicity

Glaucoma may be mediated by excitotoxicity through disruptions in glutamate transport. *OPTN* is a gene that encodes Optineurin, a protein involved in controlling glutamate receptor signaling [30]. This gene is often mutated in POAG, especially NTG [30]. Excessive glutamate overactivates N-Methyl-D-aspartate (NMDA) receptors, which especially affects RGCs in human and animal models [30]. Overstimulation of the NMDA receptors allows for an influx of too much calcium, causing apoptosis of the cells involved.

Autophagy

Autophagy also plays a role in glaucoma development. Autophagy is the process by which a cell recycles misfolded proteins or compromised organelles in order to increase cell survival [31]. It is an important response to cellular stress, including starvation, hypoxia, and oxidative damage [31]. Autophagic markers have been shown to increase in conditions of optic nerve damage such as glaucoma [32]. However, many studies provide conflicting evidence on whether this response is injurious or protective [32-36]. Further research is warranted to determine if treatments for glaucoma should aim to stimulate or inhibit autophagy.

Glaucoma and other neurodegenerative diseases

As a neurodegenerative disease, glaucoma shares similarities with other conditions in this category, such as Alzheimer's disease (AD), mixed dementia, Huntington's Disease, Amyotropic Lateral Sclerosis, and Parkinson's disease (PD). Glaucoma, like all of these diseases, becomes more common with age, progresses slowly and

insidiously, and carries a genetic predisposition [37]. Caspases that are activated in AD are likewise turned on in RGCs if the optic nerve is transected [38]. Rat models of glaucoma have activated caspase-3, which creates amyloid-beta by splitting amyloid precursor protein [38]. Amyloid-beta is toxic to neurons, and it may play a role in RGC death. This is essentially the same mechanism of Alzheimer amyloid plaque build-up in the brain. In fact, a retrospective study found that patients with POAG were more likely to develop AD than patients without POAG [39]. Glaucoma was positively associated with mixed dementia in a study of 1,168 geriatric patients [40]. In addition, PD patients were more likely to have glaucoma than their age- and sex-matched controls [41]. Interestingly, PD patients may or may not have decreased retinal nerve fiber layer thickness, but they still show visual field defects similar to those of glaucoma patients [42,43]. This growing group of studies provides evidence that age-related vision and memory deficits may be more related than previously thought.

NEUROPROTECTION IN GLAUCOMA TREATMENT

IOP-lowering drugs

As the only treatment proven effective for glaucoma, IOP reduction itself can be neuroprotective for the optic nerves by decreasing the oxidative stress, axon transport impairment, and neuroinflammation associated with IOP elevation. The five classes of drugs that treat glaucoma by lowering IOP include prostaglandin analogues, beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and cholinergic agents [44]. A meta-analysis study of 28 randomized clinical trials found that out of eight glaucoma drugs, bimatoprost (prostaglandin analog) lowered IOP the most at the peak, followed by travoprost, latanoprost, brimonidine (alpha agonist), timolol (beta-blocker), dorzolamide (carbonic anhydrase inhibitor), betaxolol, and brinzolamide [45].

Prostaglandin analogues are generally considered first-line because they are efficacious without many systemic side effects [46]. They work by increasing the outflow of aqueous humor, especially through the uveoscleral pathway [47]. However, these drugs are associated with ocular adnexal side effects, such as upper lid ptosis, levator dysfunction, and lower lid retraction [48]. They may also darken iris color and increase eyelash length [49,50]. Since some of these effects may impair visual function, they should be carefully monitored.

Beta-blockers decrease IOP by reducing aqueous humor synthesis in the ciliary epithelium. Although effective, they tend to constrict the airways and cause bradycardia, so they should be avoided in patients with asthma or decompensated heart failure [44]. Punctal occlusion after application of beta-blocker eye drops can help reduce systemic absorption.

Alpha-adrenergic agonists also decrease the production of aqueous humor. Epinephrine is a nonselective alpha-agonist that causes vasoconstriction of the ciliary body through alpha-1 effects, reducing aqueous humor synthesis. Its effect on alpha-2 receptors further decreases synthesis and also increases aqueous humor outflow through the uveoscleral pathway. Selective alpha-2 adrenergic agonists, such as brimonidine, may have an extra neuroprotective effect on RGCs through a mechanism other than IOP reduction. Brimonidine decreases NMDA receptor function and intracellular calcium by reducing cyclic adenosine monophosphate creation [51]. This dampens the glutamate excitotoxicity involved in glaucoma. In a clinical trial, low-pressure glaucoma patients treated with brimonidine were less likely to have progressive visual field loss than those treated with timolol (a beta-blocker), even though IOP decreases were similar in both treatment groups [52]. This may be because brimonidine both decreases aqueous humor production and increases its outflow or because it promotes optic nerve health independent of its capacity for IOP reduction [53-55]. The proposed neuroprotective potential of alpha-2 adrenergic agonists may benefit patients with and without increased IOP.

Additional IOP-lowering drugs include cholinomimetics, such as pilocarpine, and carbonic anhydrase inhibitors, including acetazolamide. Cholinomimetics act by contracting the ciliary muscle, which opens the TM, increasing the outflow of aqueous humor. Carbonic anhydrase inhibitors decrease production of aqueous humor. Some medications consist of drugs from two different classes, further reducing IOP.

Antioxidants

Since glaucoma is partially mediated by an increase in reactive oxygen species, antioxidant therapies have been proposed to help treat this disease. Acute ocular hypertension has been shown to reduce retinal glutathione in guinea pigs [56]. Glutathione is an antioxidant produced in the body that neutralizes destructive free radicals. The antioxidant Vitamin E increased the glutathione levels in the guinea pigs and protected their retinas from damage [56]. Other antioxidants, like Coenzyme Q10, alpha-lipoic acid, superoxide dismutase, and *Ginkgo biloba* leaf extract also decreased RGC loss in rat models of glaucoma [57]. Coenzyme Q10 decreased superoxide dismutase-2 and heme oxygenase-1 expression in glaucomatous mice, increasing RGC survival [58]. *Ginkgo biloba* leaf extract was suggested to slow visual field loss in patients with NTG over four years [59]. Further studies are needed to confirm beneficial effects in humans and compare antioxidants with more established drugs, but antioxidants appear to be promising therapeutics for glaucoma.

Adenosine receptor antagonists

Adenosine is a neuromodulator that can induce inflammation and activate microglia through the A_{2A} receptor

subtype [60]. Consequently, A_{2A} receptor antagonists are protective in many neuroinflammatory disorders, such as AD and PD [61]. An in vitro study showed that these drugs also prevented microglia activation and neuroinflammation in retinal cultures exposed to elevated hydrostatic pressure, preserving RGCs [60]. In rats, an A_{2A} receptor antagonist injected into the hippocampus successfully controlled the neuroinflammation induced by lipopolysaccharide, which activates microglia [62]. It also decreased apoptosis in the rat hippocampus induced by staurosporine [63]. The anti-inflammatory effects of adenosine receptor antagonists make these drugs potentially useful in many neurodegenerative conditions, including glaucoma.

Nicotinic acetylcholine agonists

Nicotine and acetylcholine (ACh) both have neuroprotective effects on the retinas of pigs and rats [64,65]. They are agonists of nicotinic ACh receptors, which block glutamate-induced excitotoxicity [64]. When the nicotinic ACh agonist PNU-282987 was injected into the eyes of rats an hour before an NaCl injection was used to induce glaucomatous change, the rats had significantly less RGC loss compared to control rats [66]. Nicotinic Ach agonists also play a large role in related neuroinflammatory diseases, such as AD and PD [67]. For example, administration of nicotine or nicotinic agonists to patients with AD improved attention and memory [68,69]. Nicotine may even decrease the chance of developing AD or PD [70]. This suggests that agonists of the nicotinic ACh receptors may reduce neurodegeneration in a variety of neuroinflammatory disorders.

Rho-pathway inhibitors

Rho is a cytoplasmic GTP-binding molecule that activates Rho-associated coiled-coil containing protein kinase (ROCK) in many different cells [71]. This activation leads to changes in cell morphology and motility, but it also causes inflammation, axon retraction, and growth cone collapse in neurons [71]. Myelin-associated molecules in the CNS activate the Rho-ROCK pathway, preventing mature CNS neurons from regenerating damaged axons. In glaucoma, ROCK is upregulated in conjunction with NMDA and glutamate excitotoxicity [72]. Drugs that inhibit ROCK, especially when used in conjunction with ciliary neurotrophic factor, have been shown to increase neurite outgrowth in RGCs, leading to axon regeneration [73]. This neuroprotective effect of Rho-pathway inhibitors makes them yet another candidate for glaucoma therapy.

Stem cell therapy

Since glaucoma is a disease of neurodegeneration, future treatment strategies could focus on regenerating lost tissue. Stem cell therapy has already been used in clinical trials for retinal diseases, as the eye is easy to access and relatively few cells need to be replaced [74]. In glaucoma, stem cells would replenish the RGCs that died in the optic nerve. They would need to travel down this structure and successfully connect to the LGN [75]. Although still challenging, it has been shown that neural progenitor cells transplanted intravitreally in a mouse model were able to migrate to the inner retinal layer within three weeks. These cells started to display morphology consistent with RGCs in response to daily injections of retinoic acid [76]. Retinal progenitor cells from newborn mice grafted into adult mice with degenerating retinas have even been shown to restore some light-mediated behavior in the recipients [77]. Stem cell therapy for ocular disease is a relatively new field still being studied in animals, but continued progress may eventually lead to cell-based therapies for glaucoma patients.

Neurotrophic factors

Even if transplanted cells cannot replace the degenerated RGCs, they can still secrete neurotrophic factors that promote the survival of the remaining neurons. Mesenchymal stem cells injected into the vitreous body of rats prolonged RGC survival by secreting platelet-derived growth factor [78]. They can also be modified to secrete BDNF, another neuroprotective agent [79]. Olfactory ensheathing cells also secrete many neurotrophic factors that can protect RGCs [75]. When transplanted into a rat optic nerve sheath and combined with intravitreal injections of recombinant human glial cell line-derived neurotrophic factor, these cells helped regenerate the axons of a damaged optic nerve [80]. Other neurotrophic factors, such as fibroblast growth factor-2, ciliary neurotrophic factor, neurotrophin 3, neurotrophin 4, nerve growth factor, and interleukin-10 have all been found to be neuroprotective in RGCs [81]. There is no cure for glaucoma, but these developing therapies show that disease reversal may eventually be possible.

CONCLUSIONS AND OUTLOOK

Glaucoma remains an important cause of progressive blindness that affects many people worldwide. Although it is defined primarily by optic nerve damage, the disease extends to the retina, LGN, and the occipital cortex. Neurodegeneration occurs through increased IOP and optic nerve ischemia, which causes oxidative stress, impairments in axonal transport, neuroinflammation, excitotoxicity, and autophagy.

Like many other neurodegenerative diseases, the prevalence of glaucoma increases with age. As life expectancy continues to escalate, especially in the western world, we can expect these diseases to affect our society with increasing severity. This will add even more burden to our health care system and economy, especially since there is no cure for these conditions. Our current treatments for glaucoma focus on lowering IOP, but they can only slow disease progression. Therapies in development emphasize neuroprotection, with the eventual goal of stopping the disease and even restoring function through the regeneration of neural tissue. Because glaucoma shares

similarities with many other degenerative diseases of the CNS, the progress made in this field may one day also be applied to these conditions.

Author Contributions: Angela Gauthier prepared a draft of the manuscript and Ji Liu, MD, offered guidance on the topic, outline construction, mentorship during the writing process, and critical revisions of the manuscript. This research was not funded.

REFERENCES

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. Ophthalmology. 2014;121(11):2081-90.
2. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82(11):844-51.
3. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. N Engl J Med. 2009;360(11):1113-24.
4. Mantravadi AV, Vadhar N. Glaucoma. Prim Care. 2015;42(3):437-49.
5. Yucel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. Prog Retin Eye Res. 2003;22(4):465-81.
6. Weber AJ, Chen H, Hubbard WC, Kaufman PL. Experimental glaucoma and cell size, density, and number in the primate lateral geniculate nucleus. Invest Ophthalmol Vis Sci. 2000;41(6):1370-9.
7. Gupta N, Ang L, de Tilly LN, Bidaisee L, Yücel YH. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. Br J Ophthalmol. 2006;90(6):674-8.
8. Chaturvedi N, Hedley-Whyte ET, Dreyer EB. Lateral geniculate nucleus in glaucoma. Am J Ophthalmol. 1993;116(2):182-8.
9. Wang SY, Melles R, Lin SC. The impact of central corneal thickness on the risk for glaucoma in a large multiethnic population. J Glaucoma. 2014;23(9):606-12.
10. Fingert JH, Heon E, Liebmann JM, Yamamoto T, Craig JE, Rait J, et al. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. Hum Mol Genet. 1999;8(5):899-905.
11. Aldred MA, Baumber L, Hill A, Schwalbe EC, Goh K, Karwatowski W, et al. Low prevalence of MYOC mutations in UK primary open-angle glaucoma patients limits the utility of genetic testing. Hum Genet. 2004;115(5):428-31.
12. Ortego J, Escribano J, Coca-Prados M. Cloning and characterization of subtracted cDNAs from a human ciliary body library encoding TIGR, a protein involved in juvenile open angle glaucoma with homology to myosin and olfactomedin. FEBS Lett. 1997;413(2):349-53.
13. Polansky JR, Fauss DJ, Chen P, Chen H, Lutjen-Drecoll E, Johnson D, et al. Cellular pharmacology and molecular biology of the trabecular meshwork inducible glucocorticoid response gene product. Ophthalmologica. 1997;211(3):126-39.
14. Alvarado J, Murphy C, Juster R. Trabecular meshwork cellularity in primary open-angle glaucoma and nonglaucomatous normals. Ophthalmology. 1984;91(6):564-79.
15. Shields MB. Normal-tension glaucoma: is it different from primary open-angle glaucoma? Curr Opin Ophthalmol. 2008;19(2):85-8.
16. Drance SM, Sweeney VP, Morgan RW, Feldman F. Studies of factors involved in the production of low tension glaucoma. Arch Ophthalmol. 1973;89(6):457-65.
17. Leung DY, Tham CC, Li FC, Kwong YY, Chi SC, Lam DS. Silent cerebral infarct and visual field progression in newly diagnosed normal-tension glaucoma: a cohort study. Ophthalmology. 2009;116(7):1250-6.
18. Sawada A, Rivera JA, Takagi D, Nishida T, Yamamoto T. Progression to Legal Blindness in Patients With Normal Tension Glaucoma: Hospital-Based Study. Invest Ophthalmol Vis Sci. 2015;56(6):3635-41.
19. Heijl A, Bengtsson B, Hyman L, Leske MC. Natural history of open-angle glaucoma. Ophthalmology. 2009;116(12):2271-6.
20. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol. 1998;126(4):498-505.
21. Rajendram R, Rao NA. Neuroglobin in normal retina and retina from eyes with advanced glaucoma. Br J Ophthalmol. 2007;91(5):663-6.
22. Tezel G, Wax MB. Hypoxia-inducible factor 1alpha in the glaucomatous retina and optic nerve head. Arch Ophthalmol. 2004;122(9):1348-56.
23. Mozaffarieh M, Grieshaber MC, Flammer J. Oxygen and blood flow: players in the pathogenesis of glaucoma. Mol Vis. 2008;14:224-33.
24. Ko ML, Peng PH, Ma MC, Ritch R, Chen CF. Dynamic changes in reactive oxygen species and antioxidant levels in retinas in experimental glaucoma. Free Radic Biol Med. 2005;39(3):365-73.
25. Quigley HA, McKinnon SJ, Zack DJ, Pease ME, Kerrigan-Baumrind LA, Kerrigan DF, et al. Retrograde axonal transport of BDNF in retinal ganglion cells is blocked by acute IOP elevation in rats. Invest Ophthalmol Vis Sci. 2000;41(11):3460-6.
26. Fahy ET, Chrysostomou V, Crowston JG. Impaired Axonal Transport and Glaucoma. Curr Eye Res. 2015:1-11.
27. Nakazawa T, Nakazawa C, Matsubara A, Noda K, Hisatomi T, She H, et al. Tumor necrosis factor-alpha mediates oligodendrocyte death and delayed retinal ganglion cell loss in a mouse model of glaucoma. J Neurosci. 2006;26(49):12633-41.
28. Vecino E, Rodriguez FD, Ruzafa N, Pereiro X, Sharma SC. Glia-neuron interactions in the mammalian retina. Prog Retin Eye Res. 2015;pii:S1350-9462(15)00045-2.
29. Wang K, Peng B, Lin B. Fractalkine receptor regulates microglial neurotoxicity in an experimental mouse glaucoma model. Glia. 2014;62(12):1943-54.
30. Doucette LP, Rasnitsyn A, Seifi M, Walter MA. The interactions of genes, age, and environment in glaucoma pathogenesis. Surv Ophthalmol. 2015;60(4):310-26.
31. Wang Y, Huang C, Zhang H, Wu R. Autophagy in glaucoma: Crosstalk with apoptosis and its implications. Brain Res Bull. 2015;117:1-9.
32. Koch JC, Lingor P. The role of autophagy in axonal degeneration of the optic nerve. Exp Eye Res. 2016;144:81-9.
33. Park HY, Kim JH, Park CK. Activation of autophagy induces retinal ganglion cell death in a chronic hypertensive glaucoma model. Cell Death Dis. 2012;3:e290.
34. Piras A, Gianetto D, Conte D, Bosone A, Vercelli A. Activation of autophagy in a rat model of retinal ischemia following high intraocular pressure. PLoS One. 2011;6(7):e22514.
35. Kitaoka Y, Munemasa Y, Kojima K, Hirano A, Ueno S, Takagi H. Axonal protection by Nmnat3 overexpression with involvement of autophagy in optic nerve degeneration. Cell Death Dis. 2013;4:e860.
36. Russo R, Berliocchi L, Adornetto A, Varano GP, Cavaliere F, Nucci C, et al. Calpain-mediated cleavage of Beclin-1 and autophagy deregulation following retinal ischemic injury in vivo. Cell Death Dis. 2011;2:e144.
37. Danesh-Meyer HV, Levin LA. Glaucoma as a Neurodegenerative Disease. J Neuroophthalmol. 2015;35 Suppl 1:S22-8.
38. McKinnon SJ. Glaucoma: ocular Alzheimer's disease? Front Biosci. 2003;8:s1140-56.
39. Lin IC, Wang YH, Wang TJ, Wang IJ, Shen YD, Chi NF, et al. Glaucoma, Alzheimer's disease, and Parkinson's disease:

an 8-year population-based follow-up study. PLoS One. 2014;9(9):e108938.
40. Mandas A, Mereu RM, Catte O, Saba A, Serchisu L, Costaggiu D, et al. Cognitive Impairment and Age-Related Vision Disorders: Their Possible Relationship and the Evaluation of the Use of Aspirin and Statins in a 65 Years-and-Over Sardinian Population. Front Aging Neurosci. 2014;6:309.
41. Nowacka B, Lubinski W, Honczarenko K, Potemkowski A, Safranow K. Ophthalmological features of Parkinson disease. Med Sci Monit. 2014;20:2243-9.
42. Eraslan M, Balci SY, Cerman E, Temel A, Suer D, Elmaci NT. Comparison of Optical Coherence Tomography Findings in Patients With Primary Open-angle Glaucoma and Parkinson Disease. J Glaucoma. 2015. [Epub ahead of print]
43. Tsironi EE, Dastiridou A, Katsanos A, Dardiotis E, Veliki S, Patramani G, et al. Perimetric and retinal nerve fiber layer findings in patients with Parkinson's disease. BMC Ophthalmol. 2012;12:54.
44. Cohen LP, Pasquale LR. Clinical characteristics and current treatment of glaucoma. Cold Spring Harb Perspect Med. 2014;4(6).
45. van der Valk R, Webers CA, Lumley T, Hendrikse F, Prins MH, Schouten JS. A network meta-analysis combined direct and indirect comparisons between glaucoma drugs to rank effectiveness in lowering intraocular pressure. J Clin Epidemiol. 2009;62(12):1279-83.
46. Singh K, Lee BL, Wilson MR. A panel assessment of glaucoma management: modification of existing RAND-like methodology for consensus in ophthalmology. Part II: Results and interpretation. Am J Ophthalmol. 2008;145(3):575-81.
47. Toris CB, Gabelt BT, Kaufman PL. Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. Surv Ophthalmol. 2008;53 Suppl 1:S107-20.
48. Shah M, Lee G, Lefebvre DR, Kronberg B, Loomis S, Brauner SC, et al. A cross-sectional survey of the association between bilateral topical prostaglandin analogue use and ocular adnexal features. PLoS One. 2013;8(5):e61638.
49. Lamminen H, Voipio V, Manninen T, Huttunen H. Effects of latanoprost in iris bioidentification. Acta Ophthalmol. 2009;87(5):529-31.
50. Wester ST, Lee WW, Shi W. Eyelash growth from application of bimatoprost in gel suspension to the base of the eyelashes. Ophthalmology. 2010;117(5):1024-31.
51. Dong CJ, Guo Y, Agey P, Wheeler L, Hare WA. Alpha2 adrenergic modulation of NMDA receptor function as a major mechanism of RGC protection in experimental glaucoma and retinal excitotoxicity. Invest Ophthalmol Vis Sci. 2008;49(10):4515-22.
52. Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. Am J Ophthalmol. 2011;151(4):671-81.
53. Yoles E, Wheeler LA, Schwartz M. Alpha2-adrenoreceptor agonists are neuroprotective in a rat model of optic nerve degeneration. Invest Ophthalmol Vis Sci. 1999;40(1):65-73.
54. WoldeMussie E, Ruiz G, Wijono M, Wheeler LA. Neuroprotection of retinal ganglion cells by brimonidine in rats with laser-induced chronic ocular hypertension. Invest Ophthalmol Vis Sci. 2001;42(12):2849-55.
55. Hernandez M, Urcola JH, Vecino E. Retinal ganglion cell neuroprotection in a rat model of glaucoma following brimonidine, latanoprost or combined treatments. Exp Eye Res. 2008;86(5):798-806.
56. Aydemir O, Naziroglu M, Celebi S, Yilmaz T, Kukner AS. Antioxidant effects of alpha-, gamma- and succinate-tocopherols in guinea pig retina during ischemia-reperfusion injury. Pathophysiology. 2004;11(3):167-71.
57. Song W, Huang P, Zhang C. Neuroprotective therapies for glaucoma. Drug Des Devel Ther. 2015;9:1469-79.
58. Lee D, Shim MS, Kim KY, Noh YH, Kim H, Kim SY, et al. Coenzyme Q10 inhibits glutamate excitotoxicity and oxidative stress-mediated mitochondrial alteration in a mouse model of glaucoma. Invest Ophthalmol Vis Sci. 2014;55(2):993-1005.
59. Lee J, Sohn SW, Kee C. Effect of Ginkgo biloba extract on visual field progression in normal tension glaucoma. J Glaucoma. 2013;22(9):780-4.
60. Madeira MH, Elvas F, Boia R, Goncalves FQ, Cunha RA, Ambrosio AF, et al. Adenosine A2AR blockade prevents neuroinflammation-induced death of retinal ganglion cells caused by elevated pressure. J Neuroinflammation. 2015;12:115.
61. Gomes CV, Kaster MP, Tome AR, Agostinho PM, Cunha RA. Adenosine receptors and brain diseases: neuroprotection and neurodegeneration. Biochim Biophys Acta. 2011;1808(5):1380-99.
62. Rebola N, Simoes AP, Canas PM, Tome AR, Andrade GM, Barry CE, et al. Adenosine A2A receptors control neuroinflammation and consequent hippocampal neuronal dysfunction. J Neurochem. 2011;117(1):100-11.
63. Silva CG, Porciuncula LO, Canas PM, Oliveira CR, Cunha RA. Blockade of adenosine A(2A) receptors prevents staurosporine-induced apoptosis of rat hippocampal neurons. Neurobiol Dis. 2007;27(2):182-9.
64. Iwamoto K, Mata D, Linn DM, Linn CL. Neuroprotection of rat retinal ganglion cells mediated through alpha7 nicotinic acetylcholine receptors. Neuroscience. 2013;237:184-98.
65. Wehrwein E, Thompson SA, Coulibaly SF, Linn DM, Linn CL. Acetylcholine protection of adult pig retinal ganglion cells from glutamate-induced excitotoxicity. Invest Ophthalmol Vis Sci. 2004;45(5):1531-43.
66. Iwamoto K, Birkholz P, Schipper A, Mata D, Linn DM, Linn CL. A nicotinic acetylcholine receptor agonist prevents loss of retinal ganglion cells in a glaucoma model. Invest Ophthalmol Vis Sci. 2014;55(2):1078-87.
67. Conejero-Goldberg C, Davies P, Ulloa L. Alpha7 nicotinic acetylcholine receptor: a link between inflammation and neurodegeneration. Neurosci Biobehav Rev. 2008;32(4):693-706.
68. White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology (Berl). 1999;143(2):158-65.
69. Potter A, Corwin J, Lang J, Piasecki M, Lenox R, Newhouse PA. Acute effects of the selective cholinergic channel activator (nicotinic agonist) ABT-418 in Alzheimer's disease. Psychopharmacology (Berl). 1999;142(4):334-42.
70. Fratiglioni L, Wang HX. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res. 2000;113(1-2):117-20.
71. Van de Velde S, De Groef L, Stalmans I, Moons L, Van Hove I. Towards axonal regeneration and neuroprotection in glaucoma: Rho kinase inhibitors as promising therapeutics. Prog Neurobiol. 2015;131:105-19.
72. Kitaoka Y, Kumai T, Lam TT, Kuribayashi K, Isenoumi K, Munemasa Y, et al. Involvement of RhoA and possible neuroprotective effect of fasudil, a Rho kinase inhibitor, in NMDA-induced neurotoxicity in the rat retina. Brain Res. 2004;1018(1):111-8.
73. Lingor P, Tonges L, Pieper N, Bermel C, Barski E, Planchamp V, et al. ROCK inhibition and CNTF interact on intrinsic signalling pathways and differentially regulate survival and regeneration in retinal ganglion cells. Brain. 2008;131(Pt 1):250-63.
74. Lewallen M, Xie T. Cell-based therapies for retinal degenerative diseases: a thousand strategies. J Glaucoma. 2013;22 Suppl 5:S42-5.
75. Rasmussen CA, Kaufman PL. Exciting directions in glaucoma. Can J Ophthalmol. 2014;49(6):534-43.
76. Chen G, Ma J, Shatos MA, Chen H, Cyr D, Lashkari K. Application of human persistent fetal vasculature neural progenitors for transplantation in the inner retina. Cell Transplant. 2012;21(12):2621-34.
77. Klassen HJ, Ng TF, Kurimoto Y, Kirov I, Shatos M, Coffey

P, et al. Multipotent retinal progenitors express developmental markers, differentiate into retinal neurons, and preserve light-mediated behavior. Invest Ophthalmol Vis Sci. 2004;45(11):4167-73.
78. Johnson TV, DeKorver NW, Levasseur VA, Osborne A, Tassoni A, Lorber B, et al. Identification of retinal ganglion cell neuroprotection conferred by platelet-derived growth factor through analysis of the mesenchymal stem cell secretome. Brain. 2014;137(Pt 2):503-19.
79. Harper MM, Grozdanic SD, Blits B, Kuehn MH, Zamzow D, Buss JE, et al. Transplantation of BDNF-secreting mesenchymal stem cells provides neuroprotection in chronically hypertensive rat eyes. Invest Ophthalmol Vis Sci. 2011;52(7):4506-15.
80. Liu Y, Gong Z, Liu L, Sun H. Combined effect of olfactory ensheathing cell (OEC) transplantation and glial cell line-derived neurotrophic factor (GDNF) intravitreal injection on optic nerve injury in rats. Mol Vis. 2010;16:2903-10.
81. Nafissi N, Foldvari M. Neuroprotective therapies in glaucoma: I. Neurotrophic factor delivery. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2015. [Epub ahead of print].