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Neuroprotection for Glaucoma: Requirements for Clinical Translation

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Abstract

Within the field of glaucoma research, neuroprotection is defined as slowing the functional loss in glaucoma by a mechanism independent of lowering of intraocular pressure. There is currently a great potential for research surrounding neuroprotection as it relates to glaucoma. Anatomical targets for neuroprotection should focus on upstream rather than downstream factors, and could include any part of the retinal ganglion cell, the glia, especially astrocytes or Muller cells, and vasculature. The great number of anatomical targets is exceeded only by the number of possible biochemical pathways and potential treatments. Successful treatment may be accomplished through the targeting of one or even a combination of multiple pathways. Once a treatment is shown effective *in vitro*, it should be evaluated *in vivo* with carefully chosen animal models and studied in sufficient numbers to detect statistically and clinically significant effects. Such a drug should have few systemic side effects and its delivery should be optimized so as to encourage compliance. There are still a multitude of possible screens available to test the efficacy of a neuroprotective drug and a single gold standard is ideal for the accurate assessment and comparison of new drugs. Future studies in neuroprotection should investigate the genetic component of the disease, novel pharmaceutical agents for new or known pathways, modulations of scleral biomechanics, and relation to research of other complex disorders of the central nervous system.

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[1]This article summarizes the results of a targeted session on this topic at the March 2015 conference Astrocytes and Glaucomatous Neurodegeneration. This meeting was a follow-up to the 2010 meeting on the same topic, both of which were conducted as part of The Lasker/IRRF Initiative for Innovation in Vision Science. For more information about this conference, its participants and other review articles that originated from it see Tamm and Dowling, 2016. A list of the other participants of the targeted session is provided at the end of this article.

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1. Introduction

Although intraocular pressure (IOP) lowering has been definitively shown to decrease progressive visual loss in most patients with glaucoma (Garway-Heath et al., 2015; Heijl et al., 2002), there are some patients for whom IOP lowering is either insufficient, difficult to achieve, or associated with risks of adverse effects, e.g., in the case of some surgical therapies. This is the rationale for therapies that prevent visual loss in glaucoma through mechanisms other than IOP lowering, with the most studied being neuroprotection. A recent meeting of the Lasker Foundation and International Retina Research Foundation held a workshop on what is needed for neuroprotection to be translated to clinical use. Participants in this workshop were Leonard Levin, Harry Quigley, Megan Crowe, Francesca Cordeiro, Larry Donoso, Joyce Liao, Rick Libby, Richard Masland, Rob Nickells, Paul Sieving, and Al Sommer.

This paper summarizes the wide-ranging discussion from the workshop, and will focus on potential targets of neuroprotection, biochemical pathways that could lead to new drugs, translating animal models to human studies, and the design of human trials for a hypothetical neuroprotective drug. There are a multitude of biological targets for neuroprotection and a number of these biochemical pathways show promise (Almasieh et al., 2012; Danesh-Meyer, 2011; Nickells et al., 2012). The variety of potential targets and biochemical pathways are consistent with glaucoma being an extremely complex disease, and suggests treatment of more than one type or pathway. Once a drug is developed and shows promise *in vitro*, it may be advantageous to show efficacy in more than one animal model in order to increase the likelihood of translation to large human clinical trials (Ergorul and Levin, 2013).

2. A definition for neuroprotection

In terms of drug development, there are several issues in the definition of neuroprotection. The goal of glaucoma treatment is the preservation of quality of life by decreasing the loss of functional retinal ganglion cells (RGC) and their connectivity. The lowering of intraocular pressure (IOP) has been shown to slow RGC death (Cordeiro et al., 2004) and visual field damage,(Garway-Heath et al., 2015; Heijl et al., 2002) and the amount of visual field loss is closely associated with reported quality of life and functional measures of daily living (McKean-Cowdin et al., 2008). Thus, the term, neuroprotection, is now generally defined as an approach to slowing the functional loss in glaucoma by a mechanism that is independent of and in addition to IOP lowering (Levin and Peeples, 2008). The treatment should truly slow progression and not just temporarily improve function, i.e. not simply be neuroenhancement (Chang and Goldberg, 2012). Since IOP lowering is efficacious, it will continue to be used in most, if not all, glaucoma patients, along with neuroprotective therapy, unless subsequent research shows that a new neuroprotective treatment is actually superior to IOP lowering.

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3. Potential anatomical targets

Currently, there are host of potential anatomical targets for neuroprotection in glaucoma. It is best to focus on where the damage is occurring rather than focusing on distal targets. There is considerable evidence that the initial events in glaucoma include axonal injury at the optic nerve head as a result of one or more injuries, including mechanical, vascular, biochemical, or others (Howell et al., 2007; Levin, 2001; Quigley et al., 1981; Quigley et al., 1979; Soto et al., 2008). Thus, the RGC is a primary target for neuroprotection, including its axon, cell body and dendritic tree. The RGC is contained within several milieus along its course: the retina, nerve head, optic nerve, chiasm, tract, and its central targets. Therefore, the damage process can involve interactions of RGC with glia and other neurons in the retina and targets, vascular cells in all 3 sites, and various stresses mediated by biomechanical forces at the sclera and nerve head connective tissues. Beneficial therapies may include those that improve survival mechanisms in RGCs, glia, especially astrocytes or Muller cells, and vasculature. Some studies have shown that astrocytes respond quickly to periods of increased IOP (Son et al., 2010), and it could be that these changes have both beneficial and detrimental downstream effects on RGCs (Chong and Martin, 2014; Johnson and Morrison, 2009). While secondary effects of glaucoma occur in anterograde centers, i.e., the lateral geniculate nucleus (LGN) and cortex (Gupta et al., 2009; Zhang et al., 2016), these are unlikely to have primary value as treatment targets (Danesh-Meyer and Levin, 2015). Thus, there are a variety of potential zones of interest for neuroprotective treatment. Ultimately, it may be that a drug is found for which the exact mechanism is not understood, so long as it prevents visual field deterioration and consequent decreased quality of life.

Studies that are needed include the development of rapid high-content screening techniques to identify drugs or agents targeting cells for neuroprotection. Examples include culture models of trabecular meshwork cells, RGCs, astrocytes of the optic nerve head, and scleral fibroblasts, using assays of cellular activities such as apoptosis, neurite extension, and morphological change.

4. Biochemical pathways and potential treatments

There are many potential biochemical pathways that could serve as targets for neuroprotection. A successful treatment regimen could target more than one of these pathways. One group of potential targets include neurotrophic factors such as NGF (Bai et al., 2010; Wang et al., 2014), BDNF (Mansour-Robaey et al., 1994; Martin et al., 2003), or CNTF (Ji et al., 2004) as pro-survival agents. Axon damage-induced apoptosis can be blocked with a variety of caspase inhibitors (Uchibayashi et al., 2011). Intracellular signaling of axonal damage can be interrupted with dual leucine zipper kinase (DLK) inhibitors (Huntwork-Rodriguez et al., 2013; Welsbie et al., 2013) or reduction in reactive oxygen species (Almasieh et al., 2011; Kanamori et al., 2010). Modulation of scleral rigidity via TGFβ signaling pathways can prevent mechanical effects on optic nerve head neurons or glia (Quigley et al., 2015). Gene therapy (Dahlmann-Noor et al., 2010; Johnson et al., 2010; Martin et al., 2003) can provide a mechanism to induce or repress any of the previously listed targets, while broader-acting interventions such as exercise can have wide-ranging effects (Roddy and Ellemberg, 2012). Histone deacetylase inhibitors, for example, are

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currently used for cancer treatment and are considered neuroprotective in CNS disease (Pelzel et al., 2010; Schmitt et al., 2015). Similarly, potential drugs which are already marketed for other uses include CoQ10 (which can serve as an electron carrier in the mitochondrial electron transport chain (Lee et al., 2014)), losartan (which is a selective angiotensin 1 receptor that can modulate scleral rigidity via the TGFβ pathway (Quigley et al., 2015)), and others. The vast number of biochemical pathways and potential treatments hint at the complexity of glaucoma as a disease and the potential need for multiple drugs in a treatment regimen, or alternatively, the tailoring of treatment to the dominant mechanism operative in each individual.

Techniques for rapid screening of drugs or other agents in animals should be developed, including the use of *in vivo* imaging or neuroimaging of RGCs, astrocytes, and the optic nerve. The development process would be helped by determination of how combining tests of efficacy in simpler optic nerve models could predict responses in the more challenging animal glaucoma models. Delineation of which glaucoma models are likely to be highly predictive of effects in human glaucoma would advance translatability to the clinic (Levin and Danesh-Meyer, 2010).

5. Translating animal models to humans

Once a promising drug(s) is (are) shown efficacious in *in vitro* studies, it should be tested in at least two animal models before going on to human trials. This would help in developing the dosing and delivery methods, as well as rule out species-specific effects that could make human trials unlikely to succeed. Currently, there are a number of different animal glaucoma models in use for neuroprotection, including mice, rats, beagles, pigs, and nonhuman primates. Each has advantages and disadvantages. For example, pig eyes are similar to the human, yet they are not substantially less expensive than nonhuman primates, although pigs are more available. Rodents provide a relatively inexpensive model, but are not as biologically similar to humans as nonhuman primates. Nonhuman primates are very expensive, but their eye is very similar to the human and they are critical for toxicity studies.

For clinical trials, there are important strategic choices that should be made in proposed studies before entering full-scale human phase 3 trials. An approach that would shorten the time to determine efficacy and allow human dose-response tests before a major phase 3 trial are futility designs looking for large effects (Quigley, 2012). These could narrow the search for a highly efficacious, low side-effect approach. There is rationale for proof-of-concept clinical trials of a future glaucoma drug in other optic neuropathies that might have shorter durations. Issues include obtaining baseline measurements, recruitment, and ability to randomize in a reasonable time frame. New approaches to shortening the time to see an effect on glaucomatous progression would aid in the development of neuroprotective drugs (Zhu et al., 2015; Zhu et al., 2014).

6. Dynamics of a hypothetical drug in human trials

As of yet, there is no gold-standard outcome measure for neuroprotection in a glaucoma clinical trial. All drugs approved by the US Food and Drug Administration (FDA) were

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based on efficacy of IOP-lowering. This is irrelevant for neuroprotection, for which an objective measure of visual loss, either functional or structural, is needed. Stated opinions from FDA regarding outcome measures in glaucoma so far only include visual field testing (Weinreb and Kaufman, 2011). For recruitment to a study using visual field testing, the number of subjects can be minimized if the intrasubject variability from test-to-test is low and if the intersubject homogeneity of progression rate is high. A specific proposal for study recruitment is to identify persons likely to give reliable visual field outcomes from existing records of patients at large glaucoma centers, maximizing efficiency for a study in which visual fields are the primary outcome. Studies could use structural tests, such as optical coherence tomography, as the outcome if the selected population were at an earlier stage of glaucoma where this approach is more effective. Visual field tests have a wider assessment spectrum and would be better in that regard to allowing inclusion of a more general glaucoma population.

The proposed drug should not have serious side effects for a lifelong and slowly progressive disease such as glaucoma. Although local drug delivery such as periocular and intraocular injections decrease systemic side effects, these techniques have not been used on a large scale in glaucoma, and may impact recruitment. Injections may be the best mode of delivery as they maximize adherence. Presently, human trials of an encapsulated cell suspension producing ciliary neurotrophic factor are undergoing study (Chang and Goldberg, 2012). Phase 3 clinical trials are expensive, but the return on investment for a neuroprotective glaucoma drug is likely high. Funding for clinical trials will usually be sought from industry or government, but additional sources include private donors and voluntary consortia, such as the Glaucoma Research Network. The duration of a phase 3 trial could likely range from 18 months to three years.

7. Recommendations for future studies

There are several areas that should be targeted for future research to help achieve neuroprotection in glaucoma. First, further work understanding the genetics of glaucoma should help identify novel pathways or target genes that can be approached via overexpression or knockdown (Wilson and Di Polo, 2012). Second, the continued development of novel pharmacological agents for neuroprotection, or the adaptation of pre-existing drugs towards glaucoma neuroprotection, will be useful in targeting both new and known pathways of RGC degeneration and glial activation. Third, the modulation of scleral biomechanics has the potential to alter the ocular response to IOP elevation, and thereby interfere at an early level with RGC axonal injury (Nguyen et al., 2013). Finally, there are likely similarities among neuroprotection strategies that are being developed for other complex disorders of the CNS, e.g. Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis (Dunkel et al., 2012), and that should be applied to glaucoma neuroprotection.

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- Neuroprotection in glaucoma slows functional loss independent of intraocular pressure
- Anatomical targets are retinal ganglion cells, glia, and vasculature
- Animal models must be able to detect statistically and clinically significant effects
- New clinical trial designs can detect significant effects more rapidly than before
- Future targets are genetics, novel drugs, sclera biomechanics, and other CNS diseases