Cell Tissue Res (2013) 353:201–203
DOI 10.1007/s00441-013-1672-0

EDITORIAL

Neuroprotection in glaucoma

Ernst R. Tamm · Franz Grehn · Norbert Pfeiffer

Received: 31 May 2013 / Accepted: 31 May 2013 / Published online: 28 June 2013
© Springer-Verlag Berlin Heidelberg 2013

Introduction

Glaucoma is a frequent eye disease in the elderly and the second leading cause of irreversible blindness both in developed and developing countries (Resnikoff et al. 2004). Presently, about 50 million people are blind from glaucoma worldwide, a number that has not significantly changed over the last decade (Resnikoff et al. 2004; Thylefors et al. 1995). Without a doubt, glaucoma remains an unsolved problem of high significance in ophthalmology. Glaucoma is characterized by a chronic, progressive optic neuropathy that occurs in parallel to the formation of a typical excavation of the optic nerve head. The primary damage is restricted to retinal ganglion cells and the location of initial damage appears to be at the optic disc where their axons exit the eye.

For a long time, intraocular pressure (IOP) had been suspected to cause or to contribute to axonal damage in glaucoma and since Adolph Weber introduced pilocarpine as an IOP-lowering therapy in 1876 (Weber 1876), medical therapy of glaucoma has been aimed at reducing IOP. This concept was challenged more recently, because of the observation that a significant percentage (up to 30–50 %) of patients suffering from glaucomatous neurodegeneration (Shiose et al. 1991; Anderson 2003) have IOPs in the statistically normal range of 10–21 mmHg (mean±2SD: 15.5±5.5 mmHg). Evidence for a causative or contributing role of IOP has finally been obtained through a number of randomized prospective multi-center studies that clearly identified IOP as the major risk factor for the pathogenesis of glaucoma (Collaborative Normal-Tension Glaucoma Study Group 1998a, b; Gordon et al. 2002; Kass et al. 2002; Leske et al. 2003; The AGIS Investigators 2000). Apparently, therapy that reduces IOP in patients with glaucoma is neuroprotective in the sense that it delays the structural and functional damage of retinal ganglion cell perikarya and their axons. Still, compliance to medical therapy is often unsatisfactory as daily eye-drop application is required (Reardon et al. 2011; Sleath et al. 2011). Although most patients are first treated with medical therapy, IOP-lowering operations come into play when medical therapy is no longer efficient, or when the patient is incompliant or does not tolerate topical eye drops. Presently, a large array of surgeries is available, all of which try to provide IOP reduction more than medical therapy can achieve with minimal surgical side effects. The advantage of the most effective surgical procedures is that very low IOPs (approx. 10–12 mmHg) can be achieved. In this respect, glaucoma surgery is the strongest neuroprotective measure on the basis of IOP lowering. However, surgery in glaucoma may not be successful, because of surgical complications and inappropriate wound healing. Moreover, there are only a limited number of randomized clinical trials assessing the success of surgical procedures in glaucoma (Coleman 2012).

Considering the current limits of glaucoma therapy, there is need for the development of novel and alternative treatment strategies that save retinal neurons from glaucomatous injury or have the potential to repair neurons that have already been damaged. This *Special Issue* is aimed at providing a synopsis of therapeutically strategies with the potential to act neuroprotectively in glaucoma and independently from the reduction of IOP. Another purpose of the *Special Issue* is to review the obstacles that make the translation of experimental neuroprotective therapies into clinical practice

E. R. Tamm (✉)
Institute of Human Anatomy and Embryology, University of Regensburg, Universitätstr. 31, 93053 Regensburg, Germany
e-mail: Ernst.Tamm@vkl.uni-regensburg.de

F. Grehn
Department of Ophthalmology, University Hospitals of Würzburg, Josef Schneider Str 11, 97080 Würzburg, Germany
e-mail: F.Grehn@augenklinik.uni-wuerzburg.de

N. Pfeiffer
Department of Ophthalmology, Mainz University Medical Center, Langenbeckstr. 1, 55131 Mainz, Germany
e-mail: Norbert.Pfeiffer@unimedizin-mainz.de

difficult. In addition, review articles are provided with ideas on how to overcome such obstacles. The articles presented center around the European Glaucoma Society White Paper (Tamm et al. 2013) that summarizes the results of two Think Tank Meetings organized and sponsored by the European Glaucoma Society. The White Paper highlights the current state and the perspectives of neuroprotective therapies in glaucoma. In addition to the White Paper, review articles have been selected for the *Special Issue* in which experts in the field elaborate in more detail on individual important aspects of this topic. In the following paragraphs, a brief introduction to each of the articles is provided.

Molecular approaches for neuroprotection in glaucoma

Neurotrophic molecules promote survival and differentiation of neurons. Accordingly, the application of such molecules has been shown to be very effective in preventing neuronal death in various animal models of nerve cell damage including those of the retina. Unsicker (2013) reviews the current status and the perspectives of neurotrophic molecules in the treatment of neurodegenerative diseases in the central nervous system with special focus on the retina. The article by Weber (2013) summarizes the autocrine and paracrine signaling pathways that have been shown to promote survival of retinal ganglion cells in animal models of glaucoma. Quigley and Cone (2013) provide a comprehensive review of the available evidence of the mechanisms leading to axonal damage at the optic nerve head and lamina cribrosa. On the basis of intriguing data, they propose a novel therapeutic approach that is based on the reduction of IOP-generated stress in this region by modifying extracellular matrix molecules and their metabolites in the surrounding sclera. Finally, Pfeiffer and colleagues (2013) review the neuroprotective potential of the existing medical therapy for glaucoma with special emphasis on effects that promote survival of retinal ganglion cells independently from the reduction of IOP.

Reasons for the reluctance to conduct clinical proof-of-concept studies

Even though a number of molecules have been shown to be directly neuroprotective for retinal ganglion cells in animal models of glaucoma, so far none of these molecules has found its way into clinical practice. The article by Liu and Pang (2013) reviews in detail the obstacles that are associated with bringing this kind of therapy to patients. The authors discuss the challenges in neuroprotective drug discovery, the uncertainty of medical targets and the lack of validated animal models. In addition, they identify the limitations in the clinical detection of disease progression as a major reason for the lack of clinical proof-of-concept studies.

The search for structural and functional endpoints

Glaucoma is a disease with a slow course of progression and a substantial variability between patients. Currently, the functional damage is measured by visual field assessment. Changes in the visual field occur slowly and years may be required before statistically significant changes can be detected. Clearly, if other endpoints were available, clinical studies to assess the effects of neuroprotective agents would be much easier to conduct. Werkmeister et al. (2013) review the current state of the technology available that may allow the direct imaging of retinal ganglion cells. Special emphasis is given to the methods of optical coherence tomography and adaptive optics and their current limits for the detection of retinal ganglion cells. The optical properties of retinal tissue and the potential of adaptive optics are further discussed in the article by Prasse et al. (2013). Normando et al. (2013) focus in their article on the potential of annexin-labeling for the diagnosis and follow-up of glaucoma. This method allows the visualization of those retinal ganglion cells that are in the process of apoptotic death. The potential to obtain functional endpoints by visual electrophysiology is discussed in the review article by Bach and Poloscheck (2013). The authors discuss the multifocal electroretinogram (ERG), the pattern ERG and the photopic negative response of the ERG. Finally, Rauscher et al. (2013) provide an original article in which they describe a new method to assess binocular color, motion and contrast in glaucoma.

Regeneration of retinal ganglion cells

While therapy with neuroprotective molecules is thought to augment survival of retinal ganglion cells, the challenges are higher when therapies are designed that allow replacement of already degenerated ganglion cells. Karl (2013) reviews the current state of a cell-based therapy to replace retinal ganglion cells. Another aspect of regeneration is reviewed in the article by Diekmann and Fischer (2013), which focuses on the scenario that the soma of the retinal ganglion cell is still intact while only its axon has been severed. In this review article, the potential of axonal regeneration in the glaucomatous optic nerve is discussed.

The role of Müller glia and microglia

Glial cells provide a homeostatic network that is required for the normal structure and function of retinal neurons. During injury, glial cells may switch to a reactive phenotype that

includes the secretion of signaling molecules that are both protective and damaging for retinal neurons. A more thorough understanding of this signaling network may provide novel ideas on how to protect retinal ganglion cells from damage. The article by Seitz et al. (2013) reviews the available data on the role of reactive Müller glia and microglia for the health of retinal ganglion cells.

Concluding remarks

It has been an immense pleasure and privilege to assemble this *Special Issue* of *Cell and Tissue Research* and we sincerely thank all the contributing authors as well as Klaus Unsicker who made this *Special Issue* possible and invited us to take part as guest editors. We also greatly appreciate the always very efficient and friendly help of the editorial assistant, Maite Menés. We sincerely hope that the articles presented in this *Special Issue* will stimulate the field of neuroprotection in glaucoma to promote the development of appropriate treatment strategies and their translation into clinical practice.

References

AGIS The Investigators (2000) The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 130:429–440

Anderson DR, Normal Tension Glaucoma Study Group (2003) Collaborative normal tension glaucoma study. Curr Opin Ophthalmol 14:86–90

Bach M, Poloschek CM (2013) Electrophysiology and glaucoma: current status and future challenges. Cell Tissue Res. doi:10.1007/s00441-013-1598-6

Coleman AL (2012) Advances in glaucoma treatment and management: surgery. Invest Ophthalmol Vis Sci 53:2491–2494

Collaborative Normal-Tension Glaucoma Study Group (1998a) Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 126:487–497

Collaborative Normal-Tension Glaucoma Study Group (1998b) The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol 126:498–505

Diekmann H, Fischer D (2013) Glaucoma and optic nerve repair. Cell Tissue Res. doi:10.1007/s00441-013-1596-8

Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK 2nd, Wilson MR, Kass MA (2002) The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 120:714–720, discussion 829–730

Karl MO (2013) The potential of stem cell research for the treatment of neuronal damage in glaucoma. Cell Tissue Res. doi:10.1007/s00441-013-1646-2

Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK 2nd, Wilson MR, Gordon MO (2002) The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 120:701–713, discussion 829–730

Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E (2003) Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol 121:48–56

Liu Y, Pang IH (2013) Challenges in the development of glaucoma neuroprotection therapy. Cell Tissue Res. doi:10.1007/s00441-013-1584-z

Normando EM, Turner LA, Cordeiro MF (2013) The potential of annexin-labelling for the diagnosis and follow-up of glaucoma. Cell Tissue Res. doi:10.1007/s00441-013-1554-5

Pfeiffer N, Lamparter J, Gericke A, Hoffmann E, Wahl J (2013) Neuroprotection of medical IOP lowering therapy. Cell Tissue Res. doi:10.1007/s00441-013-1671-1

Prasse M, Rauscher FG, Wiedemann P, Reichenbach A, Francke M (2013) Optical properties of retinal tissue and the potential of adaptive optics to visualize retinal ganglion cells in vivo. Cell Tissue Res. doi:10.1007/s00441-013-1602-1

Quigley HA, Cone FE (2013) Development of diagnostic and treatment strategies for glaucoma through understanding and modification of scleral and lamina cribrosa connective tissue. Cell Tissue Res. doi:10.1007/s00441-013-1603-0

Rauscher FG, Chisholm CE, Edgar DF, Barbur JL (2013) Assessment of novel binocular colour, motion and contrast tests in glaucoma. Cell Tissue Res. doi:10.1007/s00441-013-1675-x

Reardon G, Kotak S, Schwartz GF (2011) Objective assessment of compliance and persistence among patients treated for glaucoma and ocular hypertension: a systematic review. Patient Prefer Adherence 5:441–463

Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP (2004) Global data on visual impairment in the year 2002. Bull World Health Organ 82:844–851

Seitz R, Ohlmann A, Tamm ER (2013) The role of Müller glia and microglia in glaucoma. Cell Tissue Res. doi:10.1007/s00441-013-1666-y

Shiose Y, Kitazawa Y, Tsukahara S, Akamatsu T, Mizokami K, Futa R, Katsushima H, Kosaki H (1991) Epidemiology of glaucoma in Japan–a nationwide glaucoma survey. Jpn J Ophthalmol 35:133–155

Sleath B, Blalock S, Covert D, Stone JL, Skinner AC, Muir K, Robin AL (2011) The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. Ophthalmology 118:2398–2402

Tamm ER, Schmetterer L, Grehn F (2013) Status and perspectives of neuroprotective therapies in glaucoma: The European Glaucoma Society White Paper. Cell Tissue Res. doi:10.1007/s00441-013-1637-3

Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY (1995) Global data on blindness. Bull World Health Organ 73:115–121

Unsicker K (2013) Neurotrophic molecules in the treatment of neurodegenerative disease with focus on the retina: status and perspectives. Cell Tissue Res. doi:10.1007/s00441-013-1585-y

Weber A (1876) Ueber die Wirkung des Pilocarpium muriaticum. Centralbl Med Wissensch 14:769–772

Weber AJ (2013) Autocrine and paracrine interactions and neuroprotection in glaucoma. Cell Tissue Res. doi:10.1007/s00441-013-1556-3

Werkmeister RM, Cherecheanu AP, Garhofer G, Schmidl D, Schmetterer L (2013) Imaging of retinal ganglion cells in glaucoma: pitfalls and challenges. Cell Tissue Res. doi:10.1007/s00441-013-1600-3