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Clinical Issues: “Clinical use of neuro-protective strategies now and in the future”

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Core Concepts
• Neuroprotection is the relative preservation of neuronal structure and/or function.
• To be considered as neuro-protective, an agent must satisfy a number of criteria:
  • Have a specific and relevant receptor on the target tissue;
  • Have adequate penetration to reach the target tissue in pharmacologically effective concentrations;
  • Enhance neuronal survival or decrease neuronal damage in animal models;
  • Show efficacy in clinical trials
• IOP reduction is an indirect neuro-protectant in glaucoma and currently remains the only clinically proven treatment for glaucoma.
• Clinical trials in neuroprotection in glaucoma present unique challenges related to the study population and end point selection.
• The ideal glaucoma management paradigm will likely combine risk factor modification, IOP reduction, and the use of neuroprotective agents.

Glaucoma encompasses a spectrum of progressive optic neuropathies characterized by pathological degeneration of non-myelinated retinal ganglion cells (RGCs), with structural damage at the optic nerve head. Irrespective of the multitude of potential initiating insults, the common theme in the pathogenesis of glaucoma is the triggering of a cascade resulting in accelerated apoptosis of the RGCs. (Fig 1.)

The role of intraocular pressure (IOP) with regard to conversion or progression of glaucoma is well established. Currently IOP reduction by medical, laser or surgical means remains the only clinically proven treatment for glaucoma. IOP reduction could be referred to as an indirect neuroprotectant in the sense that the treatment does not act directly on RGCs. However, challenging situations arise when disease progression occurs which appears to be independent of IOP levels. In the Collaborative Normal Tension Glaucoma Study, despite IOP reduction, glaucomatos optic degeneration continued, albeit more slowly and in a smaller proportion of patients. In addition, methods to reduce IOP may potentially cause adverse side effects or treatment associated comorbidities. Thus neuroprotection as an alternative strategy for glaucoma has been sought.

Neuroprotection is the relative preservation of neuronal structure and/or function and offers potential as a complementary therapy to IOP lowering in the management of glaucoma. Given the incidence of disease progression in patients with seemingly well controlled IOP, molecular signals potentially contributing to neuronal cell death have been identified and explored, leading to numerous research areas targeting mechanisms for neuroprotection in glaucoma:
• Neurotrophic factors
• Calcium Channel antagonists
• Anti-oxidants/Free radical scavengers
• NMDA (N-Methyl-D-aspartame) Receptor antagonists
• Immune mediators
• Apoptosis inhibitors
• Gene therapy
• Stem cells

For any of these areas to be effectively translated to clinical practice, a number of criteria need to be fulfilled when evaluating a glaucoma neuro-protective agent's potential:
• Have a specific and relevant receptor target in the retina or optic nerve;
• Have adequate penetration to reach the retina or optic nerve in pharmacologically effective concentrations;
• Evidence of enhanced neuronal survival or decreased neuronal damage in animal models;
• Demonstrated efficacy in clinical trials

Despite laboratory evidence that several agents may provide neuroprotection in glaucoma, there is currently a lack of published human clinical trials on the use of the majority of these proposed agents. Trials in neuroprotection in glaucoma present unique challenges related to the study population and end point selection, and demonstrating efficacy has been difficult. The only drug to reach Phase III trials for glaucoma neuroprotection was Memantine which did not meet the trial's primary endpoint of visual field progression.

Memantine by its action at the NMDA receptor reduces calcium influx. An increase in intracellular calcium is neurotoxic through activation of calcium-dependent catabolic enzymes. Calcium channel antagonists such as nifedipine, verapamil and diltiazem have been investigated in low-tension glaucoma.

In a randomised placebo-controlled trial over 3 years, Nilvadipine slightly slowed the visual field progression, maintained the optic disc rim and increased posterior choroidal circulation.

Although it remains unclear whether the activity of calcium channel antagonists is mediated through direct action on calcium status or indirectly through improved optic nerve blood flow, any potential benefit from calcium channel antagonists must be weighed against the possibility of reducing optic nerve head perfusion pressure and potential adverse effects of ischaemic stress at the optic nerve head.

Ginkgo Biloba extract (EGb761) has putative properties as a potent antioxidant and free-radical scavenger, nitric oxide inhibitor, vasodilator, platelet-activating factor inhibitor and glutamate NMDA receptor inhibitor. However, its precise mode of action is poorly understood. Limited clinical data is available, though in some patients with low-ten-
sion glaucoma, Ginkgo Biloba extract appeared to improve the visual field or slowed visual field progression.14, 15

In a separate study, no effect on visual field was demonstrated with the use of Gingko Biloba.16

Brimonidine has been studied specifically as a neuroprotectant. In a long term, randomized clinical trial, patients with low-tension glaucoma treated with brimonidine tartrate 0.2% were less likely to have visual field progression than those treated with timolol maleate 0.5%. IOP levels were comparable between groups, suggesting a non-IOP related neuro-protective mechanism of action.17

Currently, we are some way from translating the advances in laboratory modelling to implementation of neuro-protection for glaucoma in our clinics. Nevertheless, in the future, neuroprotective agents will offer the potential for a new treatment paradigm in the management of glaucoma. A disease with multifactorial mechanisms will most likely benefit from a multifactorial treatment approach incorporating individualised treatment strategies, which will likely combine risk factor modification, IOP reduction and the use of neuroprotective agents.

References

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