Shedding some Light on Glaucoma · Dr. Alexander K. Ball's Research at McMaster

By: Jonathan M. Ng

Do not go gentle into that good night.
Rage, rage against the dying of the light.
- Dylan Thomas (1952)

Introduction to Glaucoma

As the second leading cause of blindness worldwide, glaucoma's cape of darkness covers more than 6.4 million sufferers across the globe (WHO, 1997). The dominant form of the disease is a silent stalker; it usually progresses into the severe, late stages without any obvious symptoms. By progressively obliterating neurons of the retina, it eventually leaves sufferers fumbling in the dark, dissociated from the vivid colours that paint our reality. To conquer the beast in the midst of such tenebrous times, vision researchers step forward with their well-designed experiments and powerful evidence. Shedding some light on the situation here at McMaster, Dr. Alexander K. Ball showcases his exciting findings on neuroprotective drugs and their potential use in retinal diseases like glaucoma.

Glaucoma – The Mechanism of Destruction

In the healthy eye, light enters and is first detected by photoreceptor neurons. From here, the signal is quickly relayed through processing *bipolar cells* and is passed on to retinal ganglion cells (RGC's) [See Figure 1]. The bundles of protruding RGC axons form the optic nerve, the critical bridge linking eye and brain, reception of light at the retina and perception of the signal. Glaucoma exacts its wrath upon this link. In most cases of the disease, high pressures within the eye accumulate and compress the optic nerve head. The resulting constriction is believed to cut off the RGC's vital supply of nutrients from the brain, effectively starving the neurons to death. Failure to receive this cocktail of target derived growth factors (TdGF's) causes them to initiate apoptosis: cell-suicide. To further complicate matters, RGC's have no means to replace themselves. They do not arise from neuronal stems cells and cannot divide to proliferate. On the patient's level, this permanent loss of cells is the direct cause of the partial or complete loss of sight that s/he experiences (Margolis & Schachat, 1999).

Dr. Ball's Research: The magic of target derived growth factors

Dr. Ball's research pursuits aim to stop RGC apoptosis in glaucoma and other retinal diseases. By using what he affectionately calls the "Magic Juice", concoctions of various TdGF's, he protects RGC's from their suicidal fate. To test the mixture, Ball uses a sound and solid research design. First, the optic nerve is severed in anaesthetized rats. This stops the flow of TdGF's and simulates the pathology of glaucoma. Next, varying amounts of TdGF's are injected into the vitreous humour of the eye to replace the missing growth factors. Finally, after measured periods of time, the effects of the various growth factors are determined by counting the surviving cells.

Two of these tested growth factors, glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), show promising results. After two weeks, the drugs successfully protect 24% and 34% of the cells that would have otherwise died in saline-injection control trials, respectively. However, Ball and others have already documented such successes in the literature (Klöcker et al., 1997; Koeberle & Ball, 1998; Yan et al., 1999). The revolutionary new findings arise from Ball's recent publication in *Neuroscience*. Here, he pioneers into unchartered land with the first-ever testing of neurturin's neuroprotective abilities in an animal glaucoma model (Koeberle & Ball, 2002). At first, neurturin's protective effects seem weak in comparison, producing only 19% protection. However, seeing further potential in the drug, Ball hypothesized that the three drugs acted through different cellular pathways. He rationalized that if such a hypothesis were true, synergistic protective effects would be observed. Putting the theory to the test and combining neurturin with BDNF injections, the novel concoction elicits an astonishing 76% RGC protection rate [See Diagram 2 & 3]. If such results were reproducible in human cases of glaucoma, almost three fourths of the individual's sight would be protected!

Dr. Alexander K. Ball, McMaster professor in the department of Pathology and Molecular Medicine

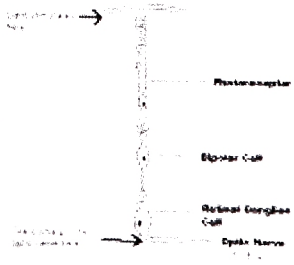
Current Research Direction: Making the right connections

Unfortunately, neuroprotection is not so simple. Although these growth factors are able to sustain RGC survival two weeks after axotomy, cell survival characteristics beyond this time period are unknown. It remains an untested theory that, once damaged, RGC's cannot escape their inevitable apoptotic fate. Although this phenomenon has not yet been thoroughly examined, the sheer complexity of the central

Figure 1:

The 3 primary cells involved in neurotransmission from the eye to the brain [photoreceptors, bipolar cells and retinal ganglion cell (RGC)] with the typical location of glaucomatous damage labelled.

Modified from http://137.222.110.150/calnet/Visual2/page2.htm



nervous system is enough to give credibility to this claim. To circumvent these potential problems, Ball hopes to take a novel approach to the rescue and regeneration of these neurons. By reconnecting RGC's to their respective brain centres after damage, he hopes to provide lasting protection that closely simulates normal physiology. Consequently, his current research is moving towards the study of neuronal dendrite and axon regrowth. With preliminary findings that the TdGF's used in his experiments produce axonal regrowth, Ball is switching to a new model of rat glaucoma that doesn't sever the guiding myelin sheath surrounding the RGC axons. The use of endothelin-1, a potent vasoconstrictor, to kill these cells would leave a guiding path for the RGC's to return to their home in the brain. The results of this experiment would have far reaching implications that extend well beyond the pathology of the eye. Successful regrowth of these neurons would imply a healing process for the numerous afflictions of the central nervous system that plague humankind.

A Candle in the Night:

With such developments now on the horizon, the future of neurological research looks exciting. For the scientific community, these contributions help map nature's hidden mysteries of neuronal protection and regeneration. Laying the groundwork for the growth knowledge worldwide, it is planting the seed for further groundbreaking discoveries. For the millions of future glaucoma sufferers, such findings offer hope for miracle drugs of the future and restoration of the gift of sight – a return to the world of vivid colour. Leading the new discoveries here at McMaster, Dr. Alexander Ball is holding a candle of hope in the night. ■

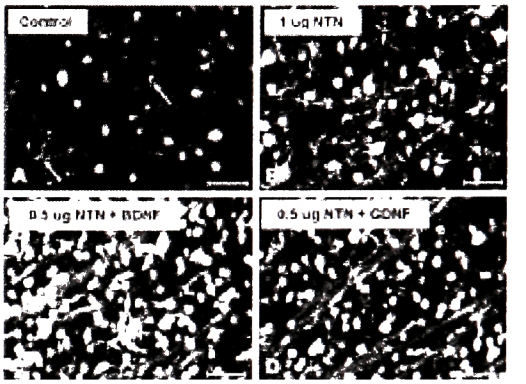


Figure 3:

Typical fluorescence confocal micrograph images of surviving RGC's after various administration of various target derived growth factors 14 days after axotomy.

(Koeberle & Ball, 2002)

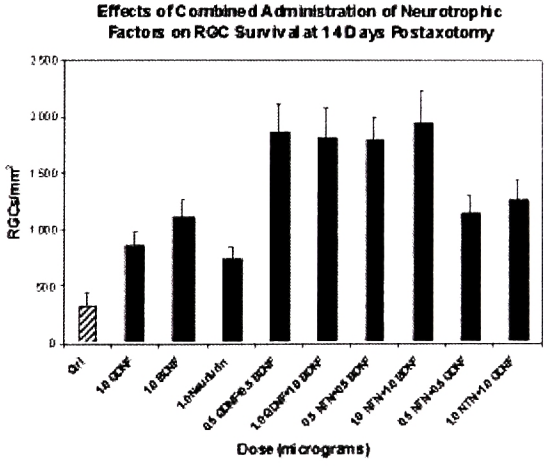


Figure 2:

Graph showing RGC survival after administration of various target derived growth factors (TdGF) 14 days after axotomy.

(Koeberle & Ball, 2002)