What’s New

Taking Retinal Neuroprotection from the laboratory to the clinic: The Glucose Story

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Core Concepts

- Naturally-occurring and inducible models of glaucoma have been used by researchers to delineate that the initial site of damage to retinal ganglion cells (RGCs) is at the optic nerve head and that this likely involves local metabolic compromise.
- In models of retinal neuron damage, preventing energy deprivation by pre-existing hyperglycaemia or intraocular delivery of glucose leads to a robust protection of RGCs.
- Hyperglycaemia also robustly protects RGCs in a rat model of laser induced-glaucoma.
- Topical glucose delivery to pseudophakic POAG patients causes temporary but significant improvement in psychophysical visual parameters such as contrast sensitivity.

Glucoma and neuroprotection

In chronic neurological diseases, like primary open-angle glaucoma (POAG), neuroprotection can be conceptualized as the reduction in the rate of neuronal loss. Currently, intraocular pressure (IOP) reduction is the only evidence-based neuroprotective strategy for all forms of glaucoma, including so-called "normal tension" glaucoma. Although IOP reduction is generally a successful strategy, some patients continue to progress despite optimal medical and surgical management. Alternative neuroprotective treatment strategies that directly protect retinal ganglion cells (RGCs), including their axons is highly clinically desirable.

Animal models of glaucoma and RGC death

Since it is unfeasible to study the initiation or progression of glaucoma at a cellular level in humans, researchers have devised a number of experimental animal models to understand better the underlying pathology (Table 1). There are also a number of other related models of RGC injury, which specifically investigate certain features of glaucoma such as models of acute IOP elevation, vessel ligation or physical RGC perikarya/axon damage.

What do laboratory studies tell us about the pathogenesis of glaucoma?

Naturally-occurring glaucoma models are useful in delineating progression

Table 1: Commonly employed animal models of glaucoma

<table>
<thead>
<tr>
<th>Type of Model</th>
<th>Animal</th>
<th>Procedure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Dogs (Beagles)</td>
<td>n/a</td>
<td>Begins at 6-12 months Autosomal recessive Excavation of ONH</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>Mutant mouse, DBA/2J</td>
<td>n/a</td>
<td>Iris pigment dispersal syndrome Maximum IOP at 11 months Sectorial RGC apoptosis</td>
</tr>
<tr>
<td>Induced</td>
<td>(Cynomolgus) Macaque monkeys</td>
<td>Argon laser-induced photocoagulation of TM</td>
<td>IOP elevation up to 11 months RGC loss Excavation of ONH</td>
</tr>
<tr>
<td>Induced</td>
<td>Mouse</td>
<td>Argon laser-induced coagulation of episcleral and limbal veins</td>
<td>Elevation of IOP from 13-20mmHg at 4 weeks RGC apoptosis by 4 weeks</td>
</tr>
<tr>
<td>Induced</td>
<td>Rat</td>
<td>Diode laser coagulation of TM and/or episcleral veins</td>
<td>Both treatments together caused IOP elevation of 6-10mmHg RGC loss up to 70% (9 weeks)</td>
</tr>
<tr>
<td>Induced</td>
<td>Rat</td>
<td>Episcleral/limbal vein cauterisation</td>
<td>IOP elevated for 3-4 months ERG a/b wave down by 3 months Focal loss of RGCs</td>
</tr>
<tr>
<td>Induced</td>
<td>Rat</td>
<td>Hypertonic saline injection into episcleral veins</td>
<td>IOP elevations of 7-28mmHg Focal RGC axon loss for low IOP elevation; total axon damage for high IOPs.</td>
</tr>
</tbody>
</table>

Notes: TM, trabecular meshwork; ONH, optic nerve head

of the disease or whether a neuroprotective treatment strategy has clinical applicability. However, inducible models provide an opportunity to investigate pathogenesis using an experimentally controlled temporal profile. By using a combination of these approaches, it has been demonstrated that RGC death is apoptotic, axons deteriorate via Wallerian degeneration, and the initial insult to RGCs likely occurs not in the retinal-based perikaryon, but in the axon at the optic nerve head (ONH), where fibres exit the eye through the lamina cribrosa. It is not clear how these mechanisms initiate RGC death, but local energetic alterations in axons, caused either by elevated metabolic demands as the metabolically fragile axons attempt to cope with increased stresses, or by decreased energy production due to lower blood flow, may play a pathogenic role. In any event, it is likely that an early consequence of changes in the local environment is a compromised RGC metabolism. Specific experimental energy deprivation to RGCs leads to their death by apoptosis, which is also the case in glaucoma.

If energy failure is part of the problem, is energy delivery part of the solution?

In light of these concepts, maintaining the energy supply to RGCs, by ensuring the continuing source of essential energy substrates even if the vascular supply is compromised, might prevent their death in glaucoma. Unusually, compared with other CNS tissues, which produce most of their adenosine triphosphate (ATP) from oxidative phosphorylation (OXPHOS), the retina makes a considerable portion of its ATP via glycolysis, even in the presence of oxygen (aerobic glycolysis). It has been hypothesised that this is due to the heavy biosynthetic load of the photoreceptors, as they constantly renew their outer segment discs. Glucose is thought to be the major energy substrate for all retinal cells. However, elevated blood glucose (hyperglycaemia) might be detrimental to hypoxic brain neurons.

We investigated retinal neuronal protection with induced hyperglycaemia. Rats were made hyperglycaemic by injecting streptozotocin, which is toxic to the insulin-producing beta cells of the pancreas. When animals were made hyperglycaemic before induction of either chronic hypoperfusion, or acute ischaemia, there was a remarkably robust preservation of both retinal structure and function. Following the success of these studies, further tests were conducted in a more relevant experimental model of glaucoma, where IOP was chronically elevated in rats by using a diode laser to photocoagulate the trabecular meshwork and limbal veins. Again, pre-existing hyperglycaemia was able to prevent much of the loss of RGCs seen at two weeks post-pressure elevation. Again the degree of protection was remarkable, with some 50% of RGC perikarya and axons preserved relative to non-hyperglycaemic controls.

From the laboratory to the clinic: Retinal neuroprotection in patients

As we demonstrated that intensive topical glucose therapy in pseudophakic patients elevated the vitreous glucose concentration, we determined whether glucose could rapidly affect vision in glaucoma patients. Two cohorts of non-diabetic pseudophakic POAG patients

Figure 1.

- Glucose
- D-Glucose
- L-Glucose

Figure 2. Log contrast sensitivity at baseline and after glucose or saline control drops
were recruited (total 40 eyes from 23 patients split into two separate studies). Eyes randomly received drops of 50% glucose or either physiological or equiosmolar saline as control, every 5 minutes for 1 hour, and contrast sensitivity was assessed as a relevant psychophysical measure of retinal function/recovery, as this parameter is impaired in POAG. Glucose had a profound effect: instillation of this monosaccharide significantly improved mean contrast sensitivity at 12 cycles/degree by 0.26 and 0.40 log units respectively in the two studies compared with saline (Fig. 1). The glucose had no effect on IOP, refraction or central corneal thickness. The effect indicates temporary neurorecovery of “sick” RGCs at the retinal level. Studies continue into most efficient means to supply glucose to deliver a sustained retinal protective effect.

**Concluding Remarks**

That glucose can offer temporary visual function recovery for POAG patients is a remarkable finding, representing the culmination of a wealth of research. Whether or not this represents a genuine therapeutic pathway is unclear. However, the results provide further evidence:

1. of energy metabolism compromise in at least some patients with POAG
2. that a portion of RGCs are sick but able to recover
3. that visual psychophysical parameters of neurorecovery can be measured rapidly and inexpensively in clinical studies.

These results motivate further bioenergetic-based neuroprotective studies in glaucoma to provide a better understanding of RGC metabolism.

**References**