

# Translational Research on BDNF may Lead to New Research Therapy in Glaucoma



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## Abstract

Glaucoma is a group of eye disorders, leading to reduction in vision and eventual blindness. Glaucoma is characterized by progressive degeneration of the retinal ganglion cells (RGCs) and optic nerve (ON) fibers. Elevated intraocular pressure (IOP) is considered as a major risk factor for glaucoma onset and progression. However, there are limitations to treating IOP exclusively, since there are patients who continue to progress with controlled low IOP. Neuroprotection by brain-derived neurotrophic factor (BDNF) may represent a new therapeutic approach independent of IOP lowering. BDNF appears to provide the highest level of protection by supporting both protective and regenerative functions in various models of ON injury and retinal diseases. However, the therapeutic approach based on BDNF is promising if the limitations imposed by complex pharmacokinetic of high molecular weight proteins (for example BDNF low propensity to pass blood-brain barrier following systemic treatment) can be overcome. Here, we discuss recent data showing that BDNF supply in the form of eye drops is able to preserve visual responses and retinal cells in experimental glaucoma.

**Keywords:** BDNF; Vision; Retinal cells; Neuroprotection

## Introduction

Glaucoma is a group of eye disorders, currently recognized to be multi factorial, progressive, leading to reduction in vision and eventual blindness. Glaucoma is characterized by progressive degeneration of the retinal ganglion cells (RGCs) and optic nerve (ON) fibers it is one of the leading causes of vision loss. Usually glaucoma affects the older population. Over 60 million people worldwide were estimated to be affected by glaucoma in 2010, and bilateral blindness from the disease was estimated to be present in 4.5 million people with glaucoma [1]. A generally accepted theory suggests an initial insult to the axons of RGCs in the ON head region, where they exit the eye [2]. Glaucoma is characterized by anomalies such as the RGC degeneration and cell death, loss of RGC axons as well as ON atrophy, impairment of visual function with visual field defects and finally loss of neurons in the lateral geniculate nucleus and visual cortex. Several types of glaucoma are known; these can be divided in primary and secondary. Primary open-glaucoma (POAG) is considered the most common subtype of glaucoma. In POAG, ocular hypertension represents the major risk factor for glaucoma onset and progression. Ocular hypertension is a

condition in which intraocular pressure (IOP) is consistently greater than normal. In the presence of ocular hypertension, there is no obvious damage to the ON as detected by an eye examination, ON imaging, or evidence of visual field changes. However, retinal responses to patterned visual stimuli (pattern electro retinogram, P-ERG) together with a transcription factor (Brn3) expressed in RGCs are altered during ocular hypertension in a murine model of glaucoma [3]. It is reasonable to think that ocular hypertension applies some stress to RGCs and their circuitry during a phase preceding the degeneration of RGCs and ON atrophy. In addition, it has been reported that the rate of untreated ocular hypertension patients in developing glaucoma was 9.5 percent in 5 years and 22 percent at 13 years [4].

There are limitations to treating IOP exclusively, including:

- i) Several glaucoma patients do not show an elevated pressure (normotensive glaucoma).
- ii) There are patients who continue to progress with controlled low IOP.

Indeed, IOP lowering by means of anti-glaucoma drugs, laser or incisional surgery is unable to arrest the progression of glaucoma till blindness.

These observations suggest that IOP-independent mechanisms contribute to disease progression, and require a new therapeutic approach independent of IOP lowering to prevent vision impairment, RGC death and ON degeneration. Neuro protection by neurotrophic factors was initially investigated for neurodegenerative diseases such as the Alzheimer's disease; evidence suggests that treatments with neurotrophic factors such as the brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-4 (NT-4) increase the survival of neurons in rodent models of injury and disease [5]. BDNF appears to provide the highest level of protection by supporting both protective and regenerative functions. The notion of a neuro protective role for BDNF in retinal degenerations derives from the observation that death of photoreceptors is prevented by intravitreal BDNF administration [6]. BDNF has been shown to protect retinal cells, in particular RGCs, in various models of ON injury and disease [7,8], interestingly, BDNF is effective in a rat glaucoma model as shown by Martin and coworkers [9] using AAV-BDNF transfection. BDNF is a high molecular weight protein locally produced by cells in the ganglion cell and inner nuclear layers [10], its TrkB receptor is expressed in RGCs, amacrine and Müller cells [10,11] that represent the cellular target of BDNF trophic action. RGC take up BDNF and transports it along axons towards target neurons and back to the cell body in the retina [12], BDNF is one of the molecules delivered to the retina by way of retrograde axonal transport [13]. These studies suggest a role for BDNF in retinal injury and diseases. A strong rationale supports BDNF treatment in glaucoma. Previous work showed that BDNF delivery to the retina is reduced in glaucoma models [13,14] and BDNF level is reduced in ocular tears [15] and blood [16]. BDNF, but not its receptor TrkB, is reduced in murine models of glaucoma [17,18]. Altogether, these studies suggest that BDNF is expressed in the retina, to help protect neurons maintaining their survival and connections when damaged by injury and diseases. Thus, neuro protection by BDNF in glaucoma can be pursued to protect RGCs. However, the therapeutic approach based on BDNF is promising if the restrictions imposed by complex pharmacokinetic of high molecular weight proteins (for example BDNF low propensity to pass blood-brain barrier following systemic treatment) can be overcome. So far BDNF, as well as other growth factors, has been typically administered to the internal ocular tissues by intravitreal or retrobulbar injection, these methods of treatment are associated with the risk of various complications such as the ocular bulb perforation and infections [19]. Given that glaucoma is a chronic condition, developing over several years, the prospect of chronic, intravitreal administration of BDNF is not realistic. To overcome these obstacles we recently settled a simple method of treatment with BDNF in the form of collyrium. We showed

that treatment for a short period with BDNF eye drops was able to increase the retinal level of BDNF in the mouse and rat retina [3]. Remarkably, BDNF topical eye treatment was able to rescue retinal responses to visual stimuli in a murine model of glaucoma during an early phase of degeneration characterized by ocular hypertension, visual impairment and RGC alterations [3]. Thus, the specific anatomical construction of the eye and, possibly, the presence of BDNF carriers offer the possibility for local drug delivery that can avoid the barriers. However, in view of therapeutic approach based on BDNF in glaucoma there are fundamental questions to be answered.

The first question is whether neuro protection by BDNF in glaucoma depends on the stage of retinal degeneration. In our previous work we showed that a short period of treatment with BDNF eye drops was able to restore vision and protect RGCs during an early phase of retinal degeneration in a murine model of glaucoma [3]. However, whether BDNF protects retinal cells at advanced stages of neuro degeneration in glaucoma is still an open question. The second question concerns the durability of BDNF neuro protective effect. Indeed, for glaucoma like other progressive neurodegenerative diseases, it is challenging to identify clinical outcome measures for use in short term proof-of-concept studies. A related question is whether BDNF treatment results in long-term neuro protective effects [20]. Previous results on this issue were contradictory. Interestingly, recent results showed that over expression of BDNF delayed progressive RGC and axon loss in hypertensive eyes [21].

The third question concerns the dose/concentration of BDNF to be used when supplied in the form of eye drops. In other words, does the topical eye application of BDNF represent a safe method of neuroprotection in glaucoma? In a previous work we used high BDNF doses to restore vision in a murine model of glaucoma [3]. This raises concerns over promotion of tumor growth resulting from BDNF taken up from non-retinal tissues; indeed, BDNF, as well as other neurotrophic factors, has been associated with neovascularization and tumor promotion [22]. To reduce the dose/concentration of BDNF we recently formulated BDNF in tamarind seed polysaccharide (TSP) [23], the TSP-BDNF combination appeared to confer a relatively higher bioavailability to BDNF.

### Future Directions

Proven neurotrophic factors such as the BDNF should be safe, effective and characterized by long-lasting protection, thus these agents can be taken to clinical trials in glaucoma and other retinal degenerations such as the Retinitis Pigmentosa and age-related macular degeneration (AMD). Drug delivery systems such as eye drops and, possibly, encapsulated cell technology, AAV-BDNF transfection should be considered for use.

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