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Role of BDNF/TrkB pathway in the visual system: Therapeutic implications for glaucoma

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Summary

Introduction—Neuroprotective therapeutics are needed to treat glaucoma, an optic neuropathy that results in death of retinal ganglion cells (RGCs).

Areas covered—The BDNF/TrkB pathway is important for RGC survival. Temporal and spatial alterations in the BDNF/TrkB pathway occur in development and in response to acute optic nerve injury and to glaucoma. In animal models, BDNF supplementation is successful at slowing RGC death after acute optic nerve injury and in glaucoma, however, the BDNF/TrkB signaling is not the only pathway supporting long term RGC survival.

Expert Commentary—Much remains to be discovered about the interaction between retrograde, anterograde, and retinal BDNF/TrkB signaling pathways in both neurons and glia. An ideal therapeutic agent for glaucoma likely has several modes of action that target multiple mechanisms of neurodegeneration including the BDNF/TrkB pathway.

Keywords

Glaucoma; BDNF; TrkB; Retinal ganglion cells; neuroprotection

Declaration of interest

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1.0 Glaucoma an optic neuropathy

Glaucoma is a progressive optic neuropathy that causes irreversible blindness and affects people throughout the world. Glaucoma is currently the second leading cause of blindness after cataracts, and the number of people afflicted with this disease is expected to rise to 79.6 million worldwide by 2020 [1,2]. Clinically, diagnosis of glaucomatous optic neuropathy is determined by the presence of both structural damage to the optic nerve and visual dysfunction [3,4]. These structural and functional changes are caused by the death of retinal ganglion cells (RGCs) and loss of their axons in the optic nerve [4]. RGCs are the final output neurons that collect visual input from the retina and transmit this information to the brain via action potentials along RGC axons [5]. RGC axons leave the retina and converge at the optic nerve head (ONH) where they pass out of the eye leaving a small depression as they form the optic nerve (ON). Loss of RGC axons combined with connective tissue alterations result in a widening and deepening of this depression that is characteristic of glaucoma [3,4].

Glaucoma is classified into two main types determined by the anatomy of the angle where the iris meets the cornea. Primary open angle glaucoma (POAG) is the most common occurring in 74% of the cases while primary closed angle glaucoma (PCAG) occurs less frequently [4]. Risk factors for glaucoma include elevated IOP, advancing age, non-Caucasian ethnicity, and a family history of glaucoma [6]. Although elevated IOP is the most significant risk factor for all types of glaucoma, elevated IOP does not always occur in glaucoma nor does lowering IOP always slow the progression of this disease [7–9]. Unfortunately, existing treatments for glaucoma are limited to eye drops, laser treatments, and surgical approaches designed to lower IOP [10]. Thus, a huge need exists for the development of neuroprotective therapeutics that will stop glaucomatous optic nerve degeneration, thereby preserving sight for millions of people.

A common characteristic of the molecular pathways implicated in glaucoma is that they lead to RGC death [11–14]. Many informative reviews have been published on mechanisms contributing to RGC apoptosis in glaucoma including mitochondrial dysfunction [15] and oxidative stress [16], endoplasmic reticulum (ER) stress and the unfolded protein response [17], neurotrophin deficits [11,18,19], excitotoxicity [20], ischemia [21], inflammation and glial activation [22,23]. Each of these pathways is a potential therapeutic target; however, our group has a keen interest in the role of brain derived neurotrophic factor (BDNF) and its cognate receptor tropomyosin-related kinase B (TrkB) in glaucoma.

In the present work, we review the relationship between the BDNF/TrkB pathway and RGC survival in the developing, healthy, and glaucomatous retina. A common theme emerges of temporal and spatial alterations in the BDNF/TrkB pathway throughout the visual system in response to RGC injury. Great strides have been made in identifying the critical role that the BDNF/TrkB signaling pathway plays in RGC survival in development and after optic nerve injury. Despite these advances, significant gaps of knowledge exist in our understanding of the molecular mechanisms that regulate the BDNF/TrkB pathway in the healthy versus glaucomatous retina. Understanding these mechanisms is difficult because the actions of the

BDNF/TrkB signaling pathway extend across multiple compartments of the visual system. In addition, much remains to be learned about the differential role of the BDNF/TrkB pathway in neurons versus glia. Future studies to better understand the function of the BDNF/TrkB pathway in the healthy versus diseased visual system will yield new insights that are essential for the development of novel therapeutic strategies to treat glaucoma.

2.0 BDNF and its receptors

BDNF is a neurotrophin that functions both within and without the central nervous system where it regulates survival, development, function, and plasticity [24]. The neurotrophin family of proteins includes four mammalian neurotrophins: nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and neurotrophin 4/5 (NT-4/5) [25–29]. The discovery of the first neurotrophin, NGF, by Rita Levi-Montalcini in the early 1950's was followed by identification of a second neurotrophin, BDNF, by Barde in 1982 [26,30]. BDNF structure and function follow a pattern similar to NGF. BDNF is synthesized as a precursor protein (~30–35 kD) that is proteolytically cleaved and processed to form mature BDNF (~14 kD) [31–33]. Proneurotrophins can either be cleaved intracellularly in the ER and Golgi by furin and proconvertases to form mature neurotrophin, or proneurotrophins can be secreted and cleaved extracellularly by plasmin and specific matrixmetaloproteases (MMPs) [34,35]. In their native state, both proBDNF and mature BDNF ligands exist as noncovalent homodimers [32]. Whether a cell secretes proBDNF, BDNF, or both varies with tissue, cell type, and culture conditions [36–38].

Neurotrophins interact with two main types of receptors: the Trk receptor tyrosine kinases and the p75 neurotrophin receptor ($p75^{NTR}$) [25,39–41]. Each neurotrophin binds to specific Trk receptors: NGF with TrkA [42], BDNF and NT-4/5 with TrkB [43,44], and NT-3 mainly with TrkC [45]. In the CNS, neuronal activity increases the localization of TrkB to the cell surface where it can bind with BDNF [46,47]. Upon BDNF binding, TrkB dimerizes and autophosphorylates which activates tyrosine kinases that initiate signaling cascades. BDNF/TrkB signaling provides trophic support and modulation of dendrites and synapse formation through three main pathways; mitogen-activated protein kinases (MAPK), phosphatidylinositol 3-kinase (PI3K), and phospholipase C-ɣ (PLC-ɣ) [40,48]. The second BDNF receptor, $p75^{NTR}$, has a much different function than TrkB. The $p75^{NTR}$ in association with Trk receptors enhances Trk receptor affinity for mature neurotrophin [49–51]. Alternatively, $p75^{NTR}$ can bind each of the neurotrophins directly, especially proneurotrophins [52,53]. The $p75^{NTR}$ does not have an intracellular kinase domain. Instead $p75^{NTR}$, which can form dimers, signals through a combination of proteolytic events and association of effector molecules with its cytoplasmic tail [41,54,55]. Although the proNGF/$p75^{NTR}$ pathway is well-known for initiating apoptosis, proBDNF activation of $p75^{NTR}$ can also cause apoptosis as well as inhibit neurite growth and spine formation (Figure 1) [34,36,56].

The modulation of the BDNF/TrkB signaling pathway is complicated by the presence of TrkB splice variants expressed throughout the CNS. Three of the most common TrkB splice variants that are expressed within the CNS are T1, T2, and T-Shc [57–60]. TrkB splice variants have a normal extracellular domain that binds BDNF but lack the intracellular

kinase domain [57–59]. Even though truncated TrkB is found abundantly in glia, it can also co-localize with full length TrkB in neurons [59,61–63]. Truncated TrkB can modulate full length TrkB signaling by inhibiting the movement of full length TrkB to the cell surface thus reducing availability of full length receptor to bind with BDNF [64]. Truncated TrkB can also act as a dominant negative receptor, forming a heterodimer with full length TrkB to prevent autophosphorylation and kinase activation of TrkB [65–68]. In addition, in non-neuronal cells, truncated TrkB can rapidly bind and internalize BDNF thereby preventing BDNF from diffusing away to adjacent cells or tissues [69]. Findings suggest that truncated TrkB may also have its own signaling functions independent of full length TrkB [70].

3.0 BDNF/TrkB in developing retina

Understanding the role of the BDNF/TrkB pathway in retinal development provides insights as to why the BDNF/TrkB pathway is important in the pathogenesis of glaucoma. RGCs are the only retinal neurons that extend their axons through the optic nerve to the brain (reviewed by Xiang, et. al., 1996 [5])Although RGC development and synapse formation is similar among vertebrates, much of our knowledge comes from studies in rodents, chicks, and tadpoles (*Xenopus*) [71]. One important difference between higher mammals such as primates and these experimental species is the distribution of RGC axon projections. In higher mammals the majority of RGC projections synapse in the lateral geniculate nucleus (LGN) with fewer axons extending to the superior colliculus (SC) [72,73]. In rodents, however, the majority of RGCs project to the SC [74], and in frogs and chicks RGCs project to the optic tectum, a brain region similar to superior colliculus in mammals [75,76]. During retinal development, RGCs are initially overproduced then undergo programmed cell death that coincides with successful formation of synapses [77–82].

In development, innervation of RGCs correlates with the spatial and temporal expression of BDNF in the visual system [83–85]. For example, in hamster, RGCs start populating the retina at embryological day 10 (E10), extend axons through the optic nerve, and arrive at the SC by E13, a time when BDNF protein levels are very low in both retina and SC [83,86,87]. BDNF levels rise in the SC (E14 to P4) as RGCs form side branches and BDNF remains high through P15 when arborization nears completion [83]. In the retina, BDNF levels do not rise until P12 to P18 when RGC axon arbors in the SC mature [83]. During the period of RGC death and synapse formation, BDNF expression is activity dependent [88]. At this time, both BDNF and TrkB mRNA and protein are expressed in retina and SC with strong BDNF and TrkB expression in RGC target areas. [83–85,89–94]. Whether BDNF/TrkB support of RGC survival during development is a result of retrograde, anterograde, or retinal sources of BDNF is a question that continues into adulthood.

Retrograde transport of target-derived BDNF in RGC survival and synapse formation is important during development. This paradigm is similar to the peripheral nervous system (PNS), where target derived BDNF is essential for the survival of select groups of neurons [95–97]. In the rodent visual system, BDNF injected into the SC decreases the rate of RGC developmental death in a manner that is consistent with retrograde transport of target-derived BDNF [98–100]. In contrast, BDNF and TrkB deficits increase the rate of RGC developmental death [101,102]. Despite BDNF/TrkB influence on the rate of RGC death,

both BDNF null mice and TrkB null mice have normal numbers of RGCs in the mature retina [101–103]. BDNF/TrkB signaling also has a critical role in formation of RGC target connections. In postnatal rats, overexpression of BDNF in the SC results in more RGC projections to the ipsilateral colliculus [104]. In addition, BDNF supplementation to the optic tectum increases the complexity of RGC arbors in developing *Xenopus* and chick [105–108]. The ability of BDNF to undergo retrograde transport from SC to RGCs continues into adulthood and has significant implications during the pathogenesis of glaucoma [109–111].

BDNF also undergoes anterograde transport from RGCs to the brain during visual system development. In developing chick and postnatal rats, intraocular injection of BDNF results in anterograde transport of BDNF from RGCs in the retina to the optic tectum and superior colliculus, respectively [112,113]. In rats, anterograde transport of BDNF increases survival of post synaptic neurons in the SC and LGN and depletion of endogenous BDNF decreases survival of these post synaptic neurons [113,114]. In addition, depletion of retinal BDNF causes RGC axons to retract from the dorsal LGN but only during development [115]. Conflicting reports exist as to whether retinal Trk receptors are required to mediate this anterograde transport [114–116]. The ability of RGCs to deliver BDNF to the SC by anterograde transport also continues into adulthood [116,117].

Endogenous production of BDNF in the retina is also important for RGC survival during development [77,100]. *In vitro* studies show that RGC survival is enhanced by BDNF produced by RGCs suggesting a role for both autocrine and paracrine BDNF/TrkB signaling in the retina [89]. Supplementation of purified RGC cultures with BDNF increases RGC survival most robustly when RGC age corresponds to the developmental time point when target innervation occurs [118,119]. BDNF also increases survival of RGCs and neurite formation in embryonic and adult retinal explants [120–122]. The important relationship between BDNF and neuronal activity with RGC survival is demonstrated in cultures from older postnatal rats (P8) in which BDNF only enhances survival when accompanied by cAMP activation [123]. The cAMP elevation, which is associated with neuron depolarization, increases TrkB levels at the RGC surface [46]. Thus, cAMP induced sensitivity of RGCs to BDNF correlates with increased availability of TrkB to bind with BDNF at the cell surface [46]. Combining a TrkB agonist with forskolin, which elevates cAMP levels, enhances the increased survival of RGCs in culture [124]. The association between electrical activity and enhanced responsiveness of RGCs to BDNF has important implications for glaucoma, where injured RGCs may be less active hence less responsive to BDNF then their healthy counterparts.

Much remains to be discovered about the interplay between retrograde, anterograde, and retinal BDNF/TrkB signaling pathways. An elegant series of studies in *Xenopus* show that during RGC development, BDNF differentially modulates RGC architecture in the retina and optic tectum depending upon the location and source of BDNF. Intraocular injection of exogenous BDNF decreases the complexity of RGC dendritic arbors but has no effect on arborization of RGC axonal projections. In contrast, tectal-derived BDNF increases the arborization of both RGC axons in the optic tectum and RGC dendrites in the retina. Thus,

BDNF can differentially modulate arbor formation of RGCs depending on the location and source of BDNF [105–107].

4.0 BDNF/TrkB in acute optic nerve injury

The importance of the BDNF/TrkB pathway in RGC development continues into adulthood, especially in response to optic nerve injury. In mature rodent retina, as in development, both BDNF and TrkB protein and mRNA are expressed in RGC and glia in the inner retina and in regions where RGC axons project in the brain [90,117,125–127]. Early studies of optic nerve injury utilized acute models such as axotomy and optic nerve crush After axotomy in rats and mice, 50–65% of RGCs die after one week, and 90% of RGCs die by 2 weeks post injury [128–130]. Similar to development, cell death after axotomy occurs by apoptosis as demonstrated by DNA fragmentation and caspase-3 expression in RGCs after axotomy [130,131]. Transient changes in BDNF/TrkB expression occur in response to optic nerve injury, however, differences in the severity of the insultmake comparisons between optic nerve crush and axatomy difficult. In rodent retinas, several studies show a BDNF gene and protein expression increase 2–5 days post injury followed by decline to control levels by 7 days post injury [132–134]. Although occasional studies do not report a decrease in BDNF expression after acute nerve injury, this may be attributable to differences in the severity of the insult [135]. In rodent retina, TrkB gene expression decreases starting at 3 days post axotomy [135,136]. TrkB deficits and ganglion cell loss are greater after optic nerve crush in mice lacking glial TrkB indicating that TrkB in glial cells plays a neuroprotective role after acute nerve injury [135]. Interestingly, in rats four weeks after axotomy, a high percentage of the few remaining RGCs are strongly TrkB positive [137]. In the SC of mice, transient increases in BDNF and TrkB have been reported in mice starting 6 hours after optic nerve crush which is earlier than in retina [133]. Overall, a general pattern emerges of an early increase in BDNF expression in response to injury followed by rapid RGC death accompanied by decreases in BDNF and TrkB expression. The pattern of BDNF and TrkB expression after acute optic nerve injury is similar to development in that the BDNF/TrkB response has spatio and temporal components closely associated with RGC survival. Alterations in the BDNF/TrkB signaling pathway appear to be an endogenous response of the retina to injury.

Numerous studies show that supplementation of the BDNF/TrkB pathway improves survival after acute optic nerve injury. In rats, BDNF exerts a strong protective effect compared to other neurotrophins [138–140]. In both rats and mice, even a single injection of BDNF significantly reduces RGC death from acute optic nerve injury [130,141,142]. In mice after axotomy, BDNF-mediated reduction in RGC death is accompanied by increased gene expression of the RGC markers Thy-1 and light neurofilament protein (NF-L), a major component of the RGC axons in the nerve fiber layer [143]. Interestingly, axotomy induced increases in GFAP, a marker of glial activation, were not reduced by BDNF treatment[143]. In cats and rats, prolonged delivery using multiple BDNF injections or virus mediated BDNF overexpression provide even greater neuroprotection, delaying RGC death for up to 6 weeks [141,144–147]. In cats, combined BDNF supplementation to both eye and visual cortex results in more RGC survival than supplementation to the eye alone [148]. In rats, BDNF supplementation in acute nerve injury is also accompanied by increased axonal

sprouting and branch length, however, BDNF does not stimulate regeneration of RGC axons into peripheral nerve grafts or the optic nerve [141,147]. In rats, TrkB gene transfer before axotomy also improves RGC survival, an effect that is amplified by a single intravitreal injection of BDNF [136]. In rats, intravitreal injections of TrkB agonists also increase RGC survival after axotomy [124,149]. The synergistic action of BDNF with TrkB overexpression underscores the need for both BDNF and TrkB to support RGC survival. Although supplementation of BDNF and TrkB after acute optic nerve injury significantly slows the rate of RGC death, BDNF and TrkB supplementation alone does not sustain long term survival. The finding that BDNF and TrkB are not the only requirements for prolonged RGC survival is not surprising. Optic nerve crush and axotomy are extreme injuries and RGCs require a complex set of nutritional requirements when maintained in purified cultures, *in vitro* [46,123].

One interesting observation from studies of acute optic nerve injury is that BDNF supplementation interacts with other factors such as the activation of microglial cells. Microglia play a central role in the CNS response to injury [150]. Whether microglia can secrete BDNF in response to optic nerve injury is unknown, however, activated microglia secrete BDNF *in vitro* and murine microglial BDNF is needed in the brain for TrkB phosphorylation, which is a mediator of synaptic plasticity [151,152]. In response to axotomy, dual effects of microglia activation in conjunction with BDNF supplementation have been reported. On one hand, in rats BDNF supplementation delays microglial activation after axotomy [153] and inhibition of microglial cells by treatment with a microglia suppressing factor enhances RGC viability and axon regeneration [154]. Whether this delay in microglial activation is a cause or effect of delayed RGC death is an area of ongoing study [155]. On the other hand, in rats, supplementation with BDNF after axotomy increases activity of nitric oxide synthase (NOS) and activates microglial cells [156,157]. Combined treatment of BDNF with a free radical scavenger or NOS inhibitor, increases BDNF mediated RGC survival after axotomy [156]. Another interesting finding is that in rats, lens injury in conjunction with axotomy protects RGCs and enhances outgrowth of RGC axons into the distal nerve [141,158–160]. This response is macrophage dependent and BDNF independent [159,160]. When BDNF is administered with lens injury and axotomy, an additive increase in RGC survival is observed, however, axon regeneration is absent [158]. The interplay between BDNF and microglia or macrophages is important in the pathogenesis of glaucoma where the final therapeutic goal is not only to prevent RGC death but to regenerate axons and restore visual function.

5.0 BDNF/TrkB in glaucoma

Although much is learned from acute models of optic nerve injury, development of more realistic glaucoma models has provided better systems with which to investigate the BDNF/TrkB pathway. A variety of rodent ocular hypertension models are available for modeling glaucoma (for reviews see [161,162]). Methods to raise intraocular pressure include restricting aqueous outflow by damaging venous drainage from the anterior chamber or by blocking the access of aqueous humor to the trabecular meshwork with microbeads. A variety of genetic mouse models are also available including the DBA2J mouse which develops ocular hypertension and glaucoma with age [163–165]. Compared to acute injury

models, glaucoma models have a slower rate of RGC apoptosis that is accompanied by damage to the optic nerve head [131]. The optic nerve head in both humans and animal models is susceptible to stress caused by ocular hypertension. As nerve fibers exit the eye at the ONH, they pass through the mesh-like lamina cribrosa that is stretched or displaced in response to changes in intraocular pressure. One cause of axonal damage in glaucoma is thought to be due to pinching of nerve fibers and blood vessels as they pass through the pores of the lamina cribrosa (reviewed in [166]).

Glaucoma induced changes in BDNF and TrkB function and expression are especially evident at the ONH. Immunohistochemical (IHC) analyses show that in healthy primate and rat eyes, BDNF and TrkB expression is relatively uniform throughout nerve bundles and connective tissue of the ONH [110,167]. In the ONH of glaucomatous primates, however, many nerve bundles have degenerated leaving accumulations of BDNF and TrkB in remaining bundles as well as in astrocytic fibers [110]. In rats, IHC analysis of BDNF expression at the ONH shows a sharp decrease in BDNF signal 7 days post onset of ocular hypertension but a week later astrocytic fibers display robust BDNF signal. Whether total BDNF/TrkB protein levels are altered or just redistributed in this region is hard to accurately access by IHC. Western blot analysis of human post mortem ONH tissue from glaucomatous eyes shows a decrease in BDNF and phosphorylated TrkB expression at the ONH that is also seen in the ONH of mice, 8 weeks post onset of ocular hypertension in a microbead model of glaucoma [168]. These observations are consistent with *in vitro* studies in which TrkB and phophorylated TrkB are reduced in lamina cribrosa and ONH astrocyte cultures after oxygen glucose deprivation [169]. Although BDNF expression in these cultures varies depending on BDNF isoform and cell type, secretion of BDNF is reduced [169]. These results highlight some of the difficulties in teasing apart the complex role of BDNF/TrkB signaling in neuronal, glial, and cribrosal elements of the ONH.

One important factor disrupting normal physiology and expression of BDNF and TrkB in the visual system is glaucoma-induced axon dysfunction. Acute increases and decreases in IOP disrupt anterograde and retrograde transport through axons of the optic nerve [170–172]. Ocular hypertension, mechanically compresses axon bundles anterior to the lamina cribrosa and causes axons posterior to the lamina cribrosa to dilate and fill with vesicles [110,170–172]. In acute ocular hypertension, BDNF transport from SC to retina is reduced and both BDNF and TrkB accumulate posterior to the ONH [110,111]. More recent studies utilizing the DBA/2J mice show that axon dysfunction and degeneration occurs before RGC loss [173–175]. How these axonal changes specifically impact RGCs and BDNF/TrkB signaling pathways throughout the visual pathway is an area of ongoing study. Another factor influencing axonal transport in the region of the lamina cribrosa is low cerebral spinal fluid (CSF) pressure. An analysis of patient data shows that low CSF pressure is correlated with normal tension glaucoma [176,177]. Low CSF pressure with normal IOP creates a trans lamina cribrosa pressure gradient similar to the pressure gradiant caused by ocular hypertension. A short term reduction of CSF pressure in rats causes a reduction in both anterograde and retrograde transport but whether lowered CSF hinders transport of BDNF from the superior colliculus to the retina has not been determined [178].

In retina, similar to the ONH, the duration and severity of glaucomatous insult influence the temporal and spatial expression of BDNF and TrkB. BDNF is expressed in inner layers of the healthy retina, especially the ganglion cell layer where it co-localizes with TrkB in RGCs [167,179]. TrkB expression in the inner retina extends throughout the NFL, GCL, and IPL with robust in signal in RGC axons [60,110,179]. In glaucomatous monkey retinas and hypertensive rats, IHC analyses show an overall reduction in BDNF signal with focal accumulations of BDNF and TrkB in the IPL. TrkB is also concentrated in the GCL [110,167]. The temporal nature of the BDNF/TrkB response to ocular hypertension combined with variation in glaucoma models make comparisons between studies difficult. In one set of studies, BDNF gene and protein expression is increased in retinas 4 weeks after episcleral vein cauterization in Wistar rats [180]. In contrast, Guo and colleagues show a general decline in BDNF gene expression that tends to correspond with increasing optic nerve damage when assayed at 5 weeks after induction of ocular hypertension in Brown Norway rats [181]. Although this trend was not statistically significant, other investigators have reported a significant decrease in BDNF gene and protein expression in mouse retina 8 weeks after induction of ocular hypertension using microbeads and laser photocoagulation [168,182]. Interestingly, in Guo's work, proBDNF protein significantly decreases with the grade of optic nerve injury. Less data is available on variation of TrkB expression with ocular hypertension. Although TrkB gene expression is reduced in retinas with more severe optic nerve injury, TrkB and pTrkB protein levels are unchanged 4–5 weeks after induction of ocular hypertension [180,181].

The importance of BDNF and TrkB deficits in the pathology of optic neuropathies is demonstrated in mice lacking one or both BDNF or TrkB allels. Although BDNF (−/−) null mice have normal numbers of RGCs in the mature retina, their axons are hypomyelinated and mice are not viable beyond three weeks of age [102]. Young heterozygous BDNF (+/−) mice have normal RGC numbers and axon myelination, yet they are more sensitive to ocular hypertension with increased visual dysfunction and loss of cells in the GCLs then wild type counterparts. By 1 year of age BDNF (+/−) mice show signs of age-related optic neuropathy. Similar to BDNF deficient mice, TrkB (−/−) null mice have normal RGC numbers with reduced myelination but are not viable after P16 [103]. TrkB (+/−) mice express 25% of normal TrkB and lose 20% of their RGCs by 3 months of age [103]. Thus, although BDNF and TrkB signaling does not determine the final number of RGCs populating the retina at the end of development, these proteins are essential to prevent RGC degeneration in adult animals.

6.0 BDNF/TrkB : Therapeutic implications

The majority of studies testing BDNF therapies in animal models of glaucoma have shown that BDNF supplementation is successful at slowing the progression of RGC degeneration. In rats, multiple intraocular injections of BDNF at weekly intervals significantly increase survival of RGCs by roughly 10% after 33 days of ocular hypertension [183]. In a more acute lasar photocoagulation model of ocular hypertension in rats, a single BDNF injection improves survival but not axonal transport for the majority of RGCs [184]. Interestingly, although BDNF treatment protects the Brn3a positive RGCs, it fails to protect the intrinsically photosensitive ganglion cells, which account for a small fraction (2.5%) of the

RGC population [184,185]. In lieu of multiple intraocular injections, which are not well tolerated in the small rodent eye, topical administration of BDNF in eye drops or BDNF gene therapy are less invasive approaches. Topical application of BDNF in the form of eye drops rescued visual function and increased numbers of Brn3a positive ganglion cells in 7 month old DBA/2J mice [186]. Although several studies have demonstrated that neurotrophins such as NGF and BDNF can be delivered to the retina and ON via eye drops, the effectiveness of this mode of neurotrophin delivery is still being validated [187]. Another strategy of BDNF delivery is to use gene therapy with adeno-associated virus (AAV) mediated BDNF overexpression systems to stimulate long term production of BDNF within the retina. BDNF overexpression rescues ganglion cells and improves visual function for at least 9 weeks after an brief and acute elevation of IOP [188]. Interestingly, BDNF synthesized by RGCs appears to have paracrine actions rescuing neighboring neurons that do not express BDNF [188]. BDNF induced protection of RGCs extends to rat glaucoma models, where BDNF overexpression leads to significant RGC survival after 4 weeks of ocular hypertension [189].

A recent study by Feng and colleagues provides hope that long-term protection of RGCs by BDNF is possible [182]. This group used a tamoxifen-induced Cre recombinase system to upregulate BDNF and to protect mouse retinas from sustained IOP elevation. Conditional BDNF overexpressing mice have reduced axon and ganglion cell loss, improved visual acuity and function, and preservation of RGC dendritic fields. Beneficial effects are maintained for up to 6 months [182]. The conditional BDNF overexpressing mice have a neuroprotective advantage over BDNF injections, topical BDNF application, and retinal AAV systems because these mice overexpress BDNF throughout their visual system. Thus, BDNF supplementation effectively occurs in retina, ONH, SC, and visual cortex simultaneously. This paper does not address the effects of BDNF overexpression in the vasculature in response to ocular hypertension, however, this factor may have therapeutic benefits as well. Although delivery of BDNF to the entire visual system is presently not possible in the human patient, the results from Feng’s study highlight the importance of understanding the role of BDNF/TrkB signaling pathway in all parts of the visual system.

Work to understand how glaucoma alters the BDNF/TrkB pathway in SC is just beginning. Two recent studies highlight the complexity of the BDNF/TrkB pathway in this region. In one study, vector-induced BDNF overexpression in the SC did not increase RGC survival or alter BDNF levels in the retina during ocular hypertension [133]. Perhaps raising BDNF levels in the SC does not guarantee transfer of BDNF to RGCs. In one of the few studies on the effect of glaucoma on the SC, Crish and colleagues use the DBA/2J model to show that BDNF accumulates in astrocytes of the glaucomatous SC, even though BDNF mRNA levels are reduced [190]. The authors propose that in response to declines in RGC axonal function, astrocytes of the SC sequester BDNF in an effort to shield target neurons from toxic insults [190]. Given the important role of BDNF/TrkB signaling in the formation of RGC arbors and synapses with SC neurons during development, a better understanding of how the structure and physiology of these connections are altered in glaucoma is critical for identifying novel therapeutic approaches. In DBA/2J mice, synapses between RGCs and neurons of the SC are maintained for a period of time after anterograde transport deficits

occur, suggesting that a therapeutic window exists for restoring RGC axonal function before synapses at the SC degenerate [190,191].

7.0 What about proBDNF?

Much remains to be learned about the function of the BDNF/TrkB pathway in both neurons and glia of the healthy and injured visual system including the role of the BDNF precursor, proBDNF. Although mature BDNF has been studied in relation to RGC survival, much less is known about proBDNF/$p75^{NTR}$ signaling pathways. Even though expression of $p75^{NTR}$ in RGCs is low, $p75^{NTR}$ expression is robust in Müller cells, the main glial cell in the retina [192,193]. As much as 80% of the total BDNF in the retina is estimated to be proBDNF [181]. Although the role of proBDNF and $p75^{NTR}$ in the glaucomatous retina is not well studied, increased $p75^{NTR}$ gene expression is accompanied by decreases in proBDNF protein in rat retinas after 5 weeks of ocular hypertension [181]. Interestingly, cultured Müller cells secrete both proBDNF and BDNF in response to treatment with glutamate, the main excitatory neurotransmitter in the retina [194]. ProBDNF's cousin, proNGF, has already been implicated in RGC death via proNGF/$p75^{NTR}$ mediated secretion of the cytokine TNF-α [193]. In addition, inhibition of $p75^{NTR}$ increases RGC survival after axotomy and this survival is enhanced by co-administration of NGF or TrkA agonist [192]. Collectively, these findings suggest that the role of proBDNF in the pathogenesis of glaucoma is an area deserving future study.

8.0 TrkB regulation and splice variants

The role of TrkB in modulating BDNF trophic support in the glaucomatous retina is not well understood and is another area deserving additional study. Although TrkB is expressed by glia and neurons of the inner retina, details regarding the cell specific localization of TrkB receptor isoforms and their role in regulation of the BDNF/TrkB signaling pathway are still emerging [195]. TrkB signaling is further complicated by the influence of modulatory proteins that associate with the TrkB cytoplasmic tail. For example, in a mouse model of glaucoma, the SH2 domain-containing phosphatase-2 (Shp-2) protein binds to the TrkB receptor in RGCs to inhibit TrkB phosphorylation [196]. This finding may explain, in part, why BDNF supplementation alone is not sufficient to rescue ganglion cells in glaucoma [196]. In glial cells, TrkB signaling plays an important neuroprotective role in response to optic nerve injury [135], however, questions regarding the role of full length versus truncated TrkB signaling remain. Future studies using glaucoma models in combination with tissue specific, conditional BDNF and TrkB knockout mice will aid in dissecting the specific roles and mechanisms of neuronal versus glial BDNF/TrkB signaling pathways in the glaucomatous retina [135,197].

9.0 Expert commentary

The importance of BDNF in human health and disease is becoming increasingly evident especially in light of findings from analyses of the human genome. Studies show that reduced levels of BDNF are associated with heart failure, cognitive disorders, and skeletal muscle energy metabolism [198–201]. Although no large studies have identified BDNF as a

biomarker for glaucoma, two small exploratory studies report BDNF deficits in tears and serum of patients with glaucoma [202,203]. The discovery that a mutation in the BDNF pro domain is present in approximately 25% of the population has significant health implications [204]. This single nucleotide polymorphism (SNP) rs6265 affects intracellular trafficking and activity-dependent secretion of BDNF and is associated with impaired memory and hippocampal function [204,205]. This same SNP, rs6265, is associated with the progression of primary open angle glaucoma in a Polish population [206]. This finding is significant in light of the current gene profiling work being done across the globe. Whether additional BDNF related genes are implicated in the progression of glaucoma remains to be seen.

Proper function of the BDNF/TrkB pathway is critical to RGC survival and visual system function in retinal development, in the adult visual system, and in response to optic nerve injury. The importance of the BDNF/TrkB pathway throughout the visual system is evident by the spatio and temporal changes in BDNF/TrkB expression during development and after optic nerve injury. These BDNF/TrkB responses are cell type and region specific extending from the retina, through the ONH, to RGC synapses with neurons of the SC. One emerging concept is that BDNF is not just important in neurons. Much remains to be learned about the differential role of the BDNF/TrkB pathway in glia. Astrocytes, Müller cells, microglia, and lamina cribrosa cells can all secrete BDNF making these cells likely players in the maintenance of healthy BDNF/TrkB signaling throughout the visual system.

Whether the BDNF/TrkB pathway is a worthy therapeutic target in glaucoma is an ongoing debate. A good therapeutic target for glaucoma should accomplish 2 goals. First, survival of RGCs needs to be preserved and second, neuronal signals between RGC axons and their targets need to be restored. Although the BDNF/TrkB pathway is not the sole source of RGC trophic support in the retina, supplementation of BDNF and TrkB in models of acute nerve injury and ocular hypertension helps to preserve RGC survival by delaying RGC death. Prevention of RGC death is the first step in neuroprotection. This neuroprotection is enhanced by combining BDNF supplementation with additional trophic factors or compounds that reduce oxidative stress.

The finding that BDNF and TrkB are not the only requirements for prolonged RGC survival should not deter scientists from trying to understand the complexities of BDNF signaling pathways that are essential for proper RGC function. Currently, our knowledge about the molecular mechanisms regulating the BDNF/TrkB pathway in glaucoma is limited. Not only does the outcome of BDNF/TrkB signaling affect interactions between the retina, ONH, and SC, but BDNF/TrkB signaling also affects the interactions between glia and neurons within each of these regions. Other areas that are highly relevant to glaucoma include modulation of full length TrkB signaling by truncated TrkB and the role of proBDNF/p75^{NTR} signaling pathways. Future studies in these areas will provide new insights that are required for the development of novel neuroprotective treatments for glaucoma.

10.0 Five year view

In the next five years, future studies into the differential roles of the BDNF/TrkB pathway in glia versus neurons will provide new insights that will aid in the development of novel

therapeutic approaches for glaucoma. An ideal therapeutic agent for glaucoma is likely to be one that has several modes of action that target multiple mechanisms of neurodegeneration including restoration of healthy BDNF/TrkB function. The ONH has high energy requirements, abundant mitochondria, and is considered the initial site of glaucomatous injury [207]. These characteristics make the ONH an ideal beneficiary of therapeutics that reduce oxidative and ER stress. A therapeutic strategy aimed at preserving function of the ONH may have the secondary effect of restoring healthy BDNF/TrkB signaling throughout the visual system. Our group is interested in sigma-1 receptor, a potential therapeutic target that meets these criteria. Sigma-1 receptor is an inter-organelle signaling modulator known to mediate oxidative and ER stress as well as BDNF processing and secretion [208–210]. A better understanding of the cellular response to stress and tissue repair will lead to new approaches to support the integrity and function of the ONH thereby hopefully preserving healthy BDNF/TrkB signaling pathways. Whether the future therapeutic agent is a sigma-1 receptor agonist or another deserving candidate, development of neuroprotective therapies for glaucoma is greatly needed to preserve vision for the many people afflicted by this sight-threatening disease.

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Key issues

- Neuroprotective therapeutics are needed to treat glaucoma.
- The BDNF/TrkB pathway is critical to retinal ganglion cell survival.
- Temporal and spatial alterations in the BDNF/TrkB pathway are a common theme.
- Duration and severity of optic nerve injury alter expression of BDNF and TrkB.
- BDNF supplementation slows RGC death after nerve injury and in glaucoma.
- The BDNF/TrkB pathway is not the only requirement for long term RGC survival.
- The interaction between retrograde, anterograde, and retinal BDNF/TrkB signaling pathways in both neurons and glia is an important area of future study.
- An ideal therapeutic agent for glaucoma will need to modulate multiple neurodegenerative pathways including the BDNF/TrkB pathway.

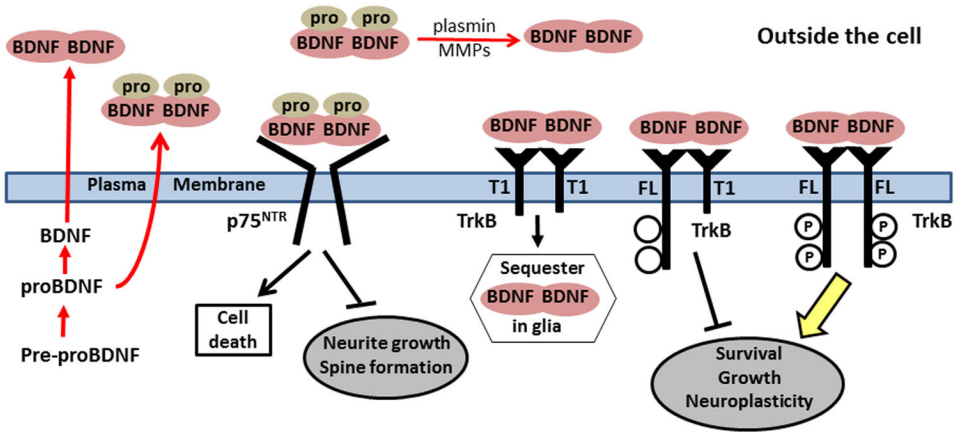

Figure 1.

BDNF signaling is a balance between proBDNF/p75^{NTR} and BDNF in glial cells or inhibit phosphorylation of FL-TrkB thereby preventing stimulation of survival, growth, and neuroplasticity.

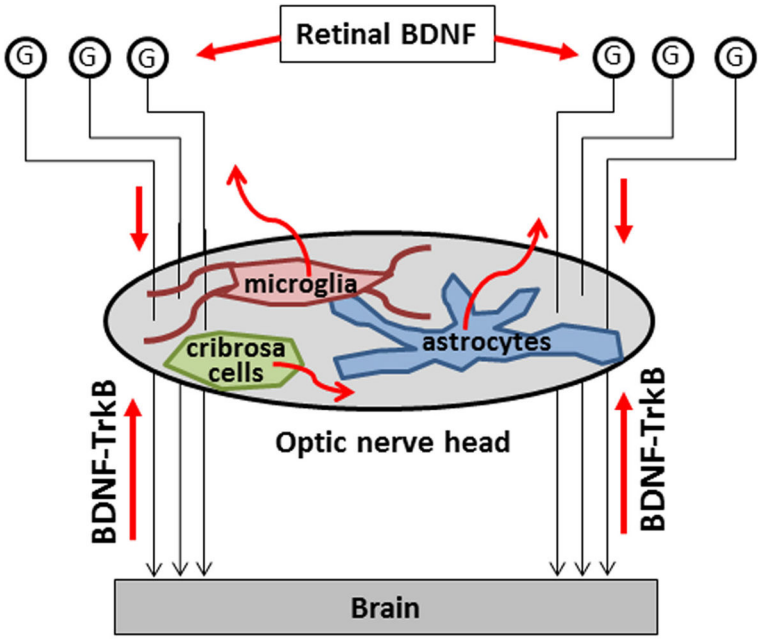

Figure 2.

BDNF is an essential neurotrophin for survival of retinal ganglion cells (G). Retrograde, anterograde and endogenous sources of BDNF are all thought to play a role in the visual system response to optic nerve injury and glaucoma.