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REVIEW ARTICLE

THE ROLE OF NEUROTROPHINS AND MIMETICS IN THE TREATMENT OF OCULAR DISEASES

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SUMMARY

The optic nerve is a bundle of fibers and axons projecting from specialized retinal neurons, the retinal ganglion cells (RGCs), which make synaptic connections to the visual cortex. Glaucoma is a chronic and progressive degenerative neuropathy of the optic nerve with death of RGCs, and is a leading cause of irreversible blindness. A risk factor for glaucoma is high intraocular pressure (IOP). However, the etiology of glaucoma is unknown and it is likely multifactorial, and upregulation of neurotoxic factors is implicated. Glaucoma can often be independent of high IOP (e.g., normal-tension glaucoma), and disease progression is independent of constant high IOP. Currently, the only pharmacological treatments approved for glaucoma are IOP-lowering drugs, which simply delay disease progression. Optic nerve neuropathy, thinning of the nerve fiber layer, degeneration of the axons, and eventual death of the RGCs continue. In the past decade, experimental therapeutic approaches have evolved to address the complex and multifactorial etiology of this disease. Two approaches are the rescue of RGCs from death by utilizing neuroprotection, and the prevention of RGC death by reducing neurotoxicity. This review draws attention to the potential of neuroprotection in glaucoma, specifically focusing on growth factors termed neurotrophins and their receptors.

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INTRODUCTION

Glaucoma is a group of optic nerve neuropathies affecting approximately 60 million people worldwide in 2010, and the number may surge to 80 million by 2020 (1, 2). Glaucoma is incurable and is characterized biologically by the chronic, progressive death of retinal ganglion cells (RGCs), and clinically by the thinning of the nerve fiber layer, progressive loss of visual field and eventual onset of blindness (3).

In the Western world, glaucoma is typically thought of as a disease caused by elevated intraocular pressure (IOP), which is the main biomarker for clinical diagnosis. However, in Eastern countries, a large proportion of patients present with normal-tension glaucoma (NTG), which is glaucoma without high IOP. Because glaucoma is otherwise indolent, it is generally not diagnosed until some visual field loss has occurred. In addition, other factors such as myopia, old age and genetic factors can impact on how glaucoma can manifest with normal IOP. For example, in some Asian populations NTG can occur in 50% of the cases (4, 5).

Reducing IOP with either drugs or surgery is the only treatment approved by the U.S. Food and Drug Administration (FDA) (6, 7). There are a variety of IOP-lowering drugs acting through various mechanisms, such as lowering aqueous humor production or enhancing draining, and some agents have dual mechanisms of action. With proper compliance, treatments are very effective at normalizing IOP, and can be beneficial because they delay further loss of vision. However, current drugs do not cure glaucoma and do not reverse the pathology. Optic nerve neuropathy, thinning of the nerve fiber layer and progressive visual field loss continue in a significant proportion of patients even if their IOP is controlled (8).

While poor compliance with dosage or administration may account for a proportion of progressing patients, the data support the theory that normalization of IOP does not provide protection to the RGCs. This notion is supported by evidence from experimental animals with glaucomatous eyes whose high IOP appears to be well controlled, yet they continue to lose RGCs at approximately half the rate of high IOP animals (9). Moreover, IOP-lowering drugs offer a poor solution to NTG patients, but are used for lack of alternatives.

Thus, while IOP is an important risk factor for glaucoma, it is not a necessary component of the disease, nor is it necessary to have constant and continuing high IOP for the disease to progress. The exact mechanisms of RGC damage in glaucoma are not well understood, and several hypotheses have been postulated. Primary (direct) damage and secondary (indirect) damage can occur, depending on specific initiating factors (10-13). Figure 1 shows possible mechanisms of primary and secondary glaucomatous damage.

What is curious is that most of the mechanisms indicated in Figure 1 should lead to *acute* RGC death, whereas glaucoma is a relatively *slow, chronic and progressive* disease of RGC death. Clearly, there is much we do not understand about the etiology and the pathological mechanisms of this disease. The field of neurobiology, which deals with other chronic neurodegenerative conditions such as Alzheimer's disease, contributes interesting comparative points for glaucoma researchers. It is worth noting that Alzheimer's disease and glaucoma may share many mechanisms (age-associated, impaired vesicular transport along neuronal fibers, vascular effects, glial activation, neurotoxic factors such as TNF-α, glutamate excitotoxicity, autoimmunity and β-amyloid [Aβ]) (14-16). Indeed, several reviews have compared glaucoma and Alzheimer's disease based on these similarities (10, 17-21).

Both glaucoma (22) and Alzheimer's disease (23) have been proposed as indications where neuroprotection would be desirable. In this review, we focus primarily on the hypothesis of neurotrophin (NT) deprivation and possible strategies for the utilization of neuroprotection, including modulation of NTs, the administration of NT analogues and the use of biological response modifiers of the NT receptors.

WHAT IS NEUROPROTECTION?

Neuroprotection refers to the use of any therapeutic modality that prevents, retards or reverses neuronal cell death resulting from primary and secondary neuronal lesions (10, 19, 20, 24). This concept is original to neurobiology, but can be expanded to optic nerve neuropathies such as glaucoma.

The visual system is part of the central nervous system, and the RGCs are specialized neurons in the retina. RGCs project fibers and axons that coalesce to form the optic nerve, through which the visual signals are electrically transmitted to the visual cortex. Broadly speaking, neuroprotection in the retina targets cells which are in danger, but does not necessarily target the initial cause of death, such as elevated IOP or elevated neurotoxic agents such as TNF-α

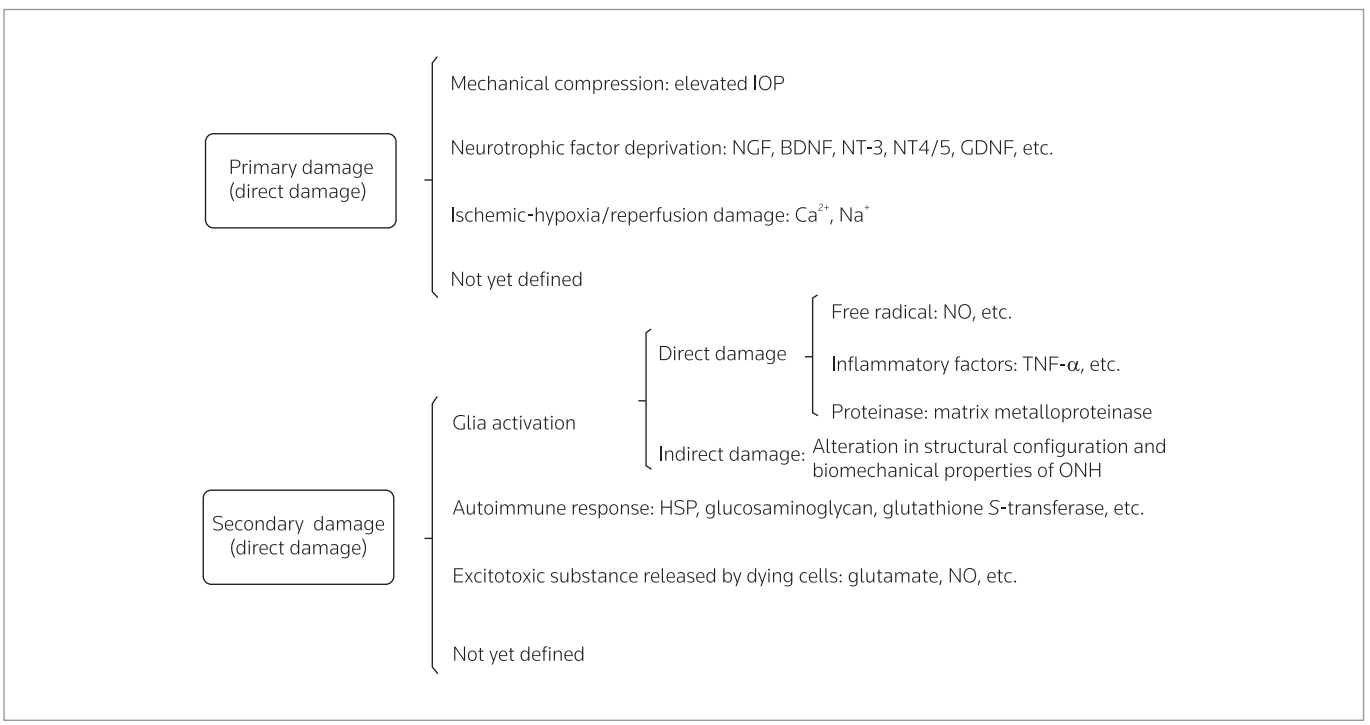

Figure 1. Possible mechanisms of primary and secondary glaucomatous damage. The mechanism of retinal ganglion cell (RGC) death in glaucoma is composed of primary damage (direct damage) and secondary damage (indirect damage). Direct damage can consist of mechanical compression of the optic nerve head (ONH) due to severe intraocular pressure (IOP), deprivation of neurotrophic factors due to impaired retrograde transport, and/or ischemic-hypoxia/reperfusion damage. The direct effects of elevated IOP likely cause altered gene expression that then leads to the indirect and long-lasting damaging effects that are independent of severe IOP. This hypothesis has been proven in several cases (e.g., β-amyloid and α_2-macroglobulin), and can explain continuous RGC death and vision loss even when high IOP has been normalized. Indirect damage can consist of glial activation and secretion of toxic factors such as TNF-α, α_2-macroglobulin, β-amyloid, glutamate excitotoxicity and autoimmunity, all of which are "shared" with Alzheimer's disease. NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; NO, nitric oxide; HSP, heat shock protein.

(12, 25, 26). Consequently, it should be possible to develop neuroprotection strategies that are synergistic or complementary with reduction of high IOP and neurotoxicity.

DO WE REALLY NEED NEUROPROTECTION IN GLAUCOMA?

In the past 10 years, research on neuroprotection as applicable to the clinical treatment and basic research of neurodegenerative diseases has generated promising results. A simple search in PubMed for "glaucoma and neuroprotection" yields over 200 items.

A large-scale clinical trial using a repositioned Alzheimer's disease drug, memantine, was carried out to purportedly deliver "neuroprotection". The failure of this clinical trials raised questions as to whether neuroprotection will benefit patients with glaucoma. This failure has done significant damage to the case for neuroprotection. In our opinion, memantine was incorrectly labeled as neuroprotective, given its dose-dependent mechanism of action, which at the doses used mostly acts as an NMDA receptor antagonist. Moreover, the concept of using memantine for glaucoma was also flawed, in our opinion, based on the patchy expression patterns of the specific NMDA receptor subunits that would have been the molecular target of this drug.

The only proven and standard therapy for glaucoma is to lower patients' IOP using medication or surgery (6, 7, 27-29). However, the effect of this long-used strategy is currently in question. More than 60% of patients lose vision despite well-controlled IOP (29-32). Moreover, nearly 30% of glaucoma patients worldwide with NTG have no effective recourse (30, 33).

Animal models of glaucoma are used to study the relationship between IOP, loss of nerve fiber layer, loss of RGCs and loss of vision. Studies have shown that injecting neurotoxic agents such as glutamate, α_2-macroglobulin, TNF-α, nitric oxide or interleukin-1 can induce glaucomatous effects that include RGC death without elevated IOP (9, 34-39). Neutralizing any one of these factors in experimental glaucoma models is partially protective to RGCs, likely because they prevent neurotoxicity. These results support the view that prevention of neurotoxicity may be a valid strategy. How about a more direct strategy that induces neuroprotection?

WHAT ARE NTs AND THEIR RECEPTORS?

NTs are a family of polypeptide growth factors (40, 41) that play a crucial role in regulating neuron biology, including cell development, fate, growth, differentiation and regeneration (42). In a single neuron, NTs may induce a broad spectrum of stimuli, including cell body growth, dendrite formation, axon elongation and synapse remodeling (43), as illustrated in Figure 2.

NTs are synthesized chiefly by three sources. The first is the target tissue innervated by the neuron. For RGCs, the cells of the visual cortex are the target tissue which provides the innervating RGCs with positive selection due to the survival- and synaptic-promoting action of NTs. The RGCs can transport the neurotrophin receptor and the neurotrophin signals retrogradely to the cell soma in the retina. The second is a local source, consisting of NTs secreted in a paracrine manner by cells neighboring the neuron (mostly glia). The third is immune cell-derived, in which cells migrate to the injury site after neuronal damage (42, 44, 45).

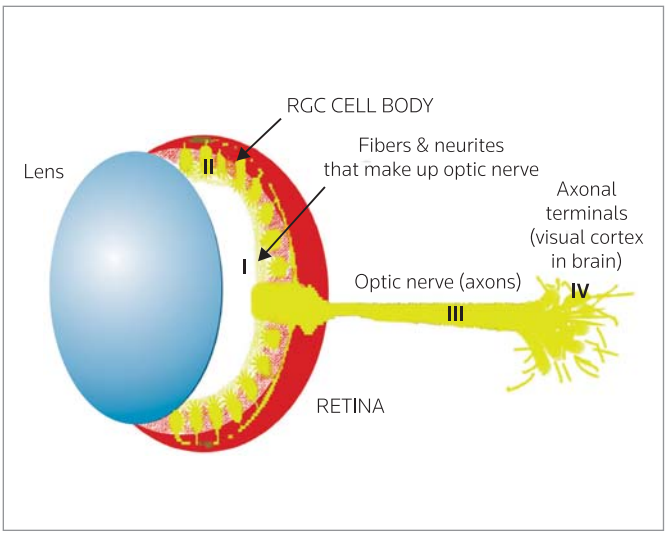

Figure 2. Neurotrophins (NTs) act at different segments of the neuron. Within the neuronal topography, NTs signal towards different fates. The NTs can be found intravitreally (position I), where they bind to fibers or cell bodies, at the cell body (position II), within axons (position III), or released by target tissue in the visual cortex (position IV). I. Ligand binding receptors at neuritic fibers and dendrites. NTs govern plasticity, growth and cross-talk to other cells within the retina. II. Ligand binding receptors at retinal ganglion cell (RGC) body. NTs determine the survival/death and differentiation state. III. Within the axon, vesicles transport NT/receptor complexes towards the cell body after they are internalized at the nerve terminals. Within these vesicles the receptors continue to signal. NT signals guide elongation and regeneration. IV. Ligand binding receptors at synaptic terminals. NTs govern plasticity, structure, activity, differentiation state and transmitter release.

The mature, fully processed form of biologically active NTs consists of a dimer of polypeptide chains, each of which has three intrachain disulfide bridges (46), as illustrated in Figure 3. Mature NTs are processed from the precursor, pro-NTs, which contain a peptide that is cleaved. The function of the pro-NTs is entirely different from the mature form in that pro-NTs usually induce cell death (47-50).

To date, four NTs have been identified in mammals: nerve growth factor (NGF) (51), brain-derived neurotrophic factor (BDNF) (52), neurotrophin-3 (NT-3) (53) and neurotrophin-4/5 (NT-4/5) (54). Each NT utilizes two cell-surface receptors. One receptor is a tropomyosin-related kinase (Trk) of the family of receptor tyrosine kinases (TrkA, TrkB and TrkC) (55). The Trk receptor is comprised of an extracellular domain, a single transmembrane domain and a single cytoplasmic tyrosine kinase domain. As shown in Figure 3, Trk family members exhibit ligand selectivity properties, i.e., NGF binds TrkA, BDNF and NT-4 activate TrkB, and NT-3 prefers TrkC but can also dock with TrkA and TrkB.

The Trk receptors relay trophic signals through ERK, Akt and phospholipase PLC-γ, as shown in Figure 4. Several truncated isoforms of TrkB and TrkC that lack the tyrosine kinase domain have been identified. These truncated receptors bind the corresponding NT and may have scavenger or dominant-negative functions. Recent work has shown that truncated Trks actually signal, but differently than

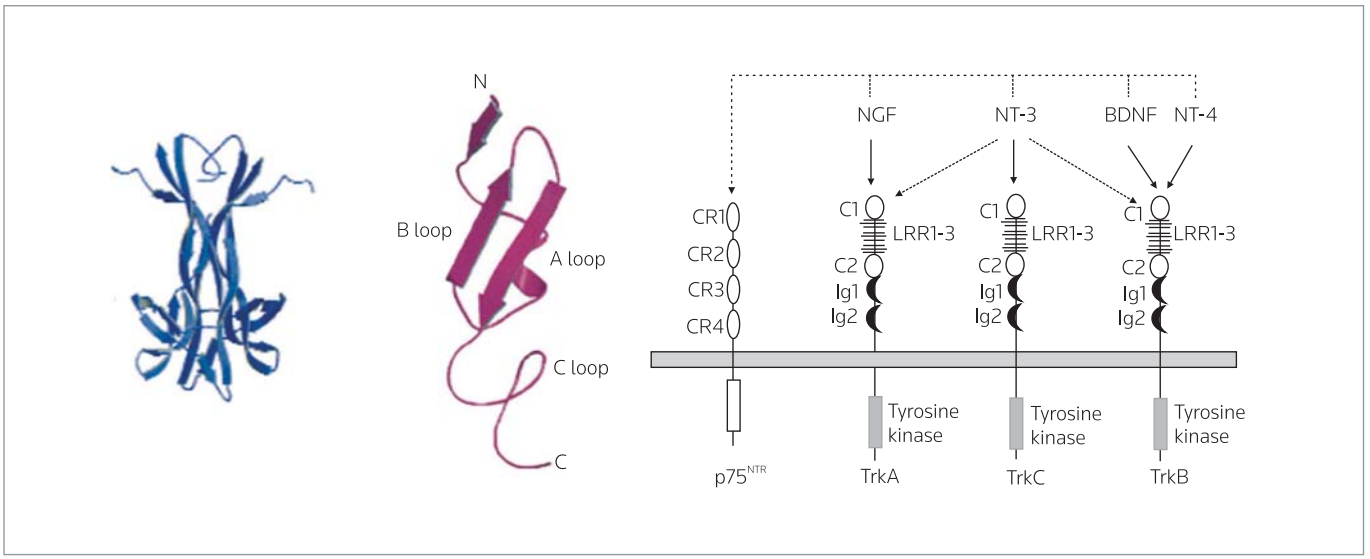

Figure 3. Neurotrophin (NT) structure and selectivity of NT receptors. Nerve growth factor (NGF) binds TrkA, brain-derived neurotrophic factor (BDNF) and NT-4 dock with TrkB, and NT-3 can bind TrkA, TrkB and mainly TrkC. All four NTs can bind $p75^{NTR}$, as do also all the pro-NTs. Adapted and reproduced from Skaper, S.D. *The biology of neutrophins, signialling pathways, and functional peptide mimetics of neurotrophins and their receptors*. CNS Neurol Disord Drug Targets 2008, 7(1): 46-62, with permission from Bentham Science Publishers Ltd.

the full-length isoforms (56). The evidence suggests that truncated Trks are deleterious to neurons.

The second receptor is the p75 receptor ($p75^{NTR}$), which belongs to the TNF receptor superfamily. $p75^{NTR}$ governs cell survival or death, depending on the cell context. All four NTs can bind equally to $p75^{NTR}$, and all pro-NTs bind exclusively to $p75^{NTR}$ and induce cell death (50, 57) (Fig. 4).

The mechanisms of cell death following the activation of $p75^{NTR}$ remain less well understood than the fact that the Trk signaling pathway accounts for the pro-survival effects. Cross-talk between $p75^{NTR}$ and other proteins such as LINGO or Nogo and Trks through ARMS (ankyrin-rich membrane spanning) (58-62) and the many adaptors downstream of $p75^{NTR}$ render the mechanism of $p75^{NTR}$-mediated death very complicated (Fig. 4).

WHAT IS THE EVIDENCE FOR NT DEPRIVATION IN GLAUCOMA?

Among the many hypotheses for the etiological factors in glaucoma, NT deprivation is one with a fair amount of evidence (3). Elevated IOP mechanically compresses the optic nerve head (ONH) and the distorted lamina cribrosa blocks the axoplasmic transport (retrograde and anterograde transport). Hence, the retrograde transport of NTs from the target tissue in the superior colliculi and lateral geniculate nuclei is prevented.

Direct evidence includes the accumulated BDNF behind the ONH (63), which cannot be effectively transported to the RGC cell body. Indirect evidence includes the fact that when apoptotic death of RGCs is induced (64), exogenous administration of NTs + NT receptors or Trk agonists, or blocking p75 with antagonists, can protect RGCs (9, 45, 65-68). There is also a good correlation where deprivation of NTs by antagonism or neutralization results in RGC death (69).

In disease states, however, there is increased expression of NT locally in retina (70, 71). The locally produced NTs do not appear to be effective at preventing RGC death. It cannot be excluded, however, that some of the upregulated NTs are actually pro-NTs that can be deleterious to some cell types. Indeed, treatment with pro-NGF causes RGC death (39).

WHAT IS THE RATIONALE FOR NEUROPROTECTION THROUGH NTs AND THEIR RECEPTORS?

Having demonstrated the evidence for the NT deprivation hypothesis, we ask what the rationale is for neuroprotection during glaucomatous damage. Previously published studies have concluded that after elevation of IOP in animal models, TrkA, TrkB, TrkC (mainly a truncated isoform of TrkC, TrkC.T1) and $p75^{NTR}$ are upregulated in both mRNA and protein (71).

TrkA, TrkB and full-length TrkC are generally thought to play a positive role in RGC survival. However, the function and signaling pathway for TrkC.T1 is expected to be deleterious (56, 72). Indeed, targeted deletion of TrkC.T1 makes RGCs resistant to glaucomatous death when high IOP is induced. TrkC.T1 is expressed by activated glia, where it helps to upregulate the production of soluble proteins such as α_2-macroglobulin and TNF-α, which are neurotoxic and can kill RGCs (73).

Neurotoxicity induced by TNF-α was reported to take place directly through TNF-α receptors present in RGCs (74). However, neurotoxicity induced by α_2-macroglobulin is more complex and has multiple mechanisms. The α_2-macroglobulin protein has receptors on RGCs, termed LRP-1, which are also receptors for clearance

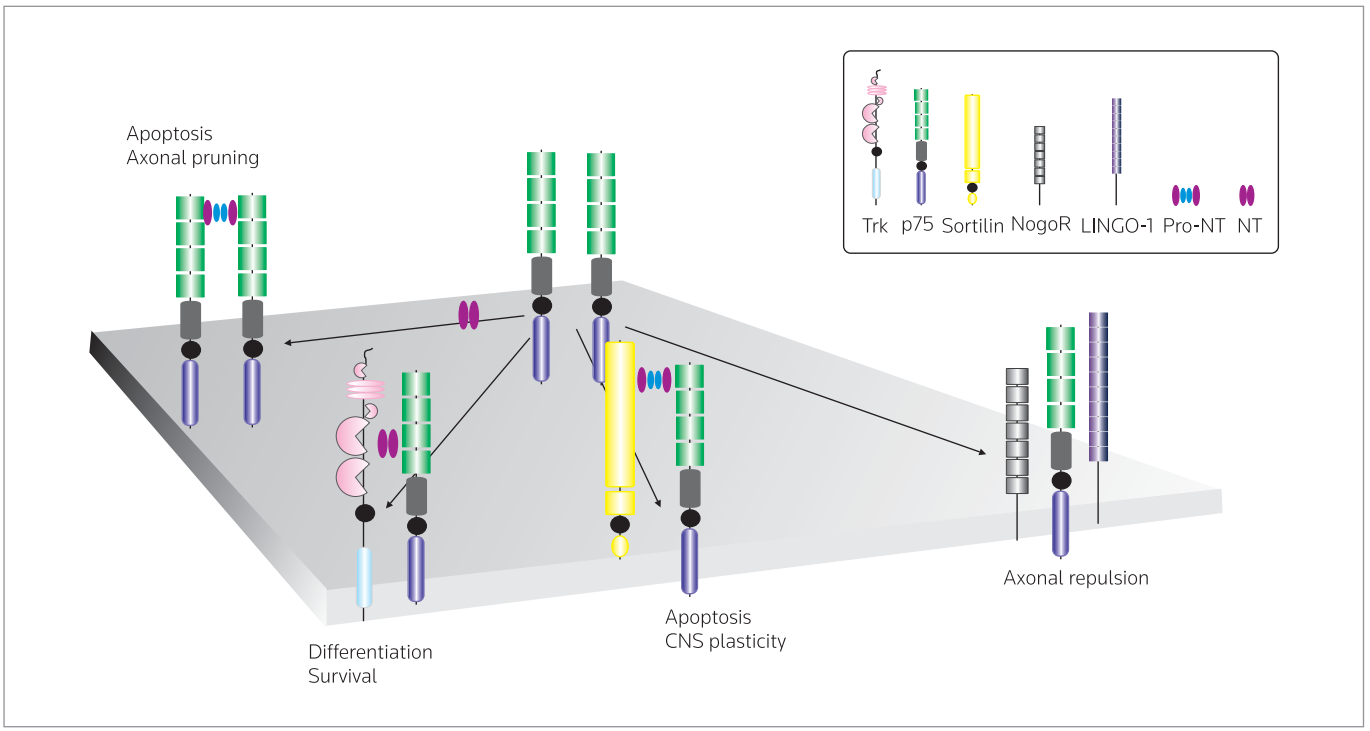

Figure 4. Signaling pathways through Trk and $p75^{NTR}$ receptors. The signaling pathway through the Trk receptor is through ERK, Akt and PLC-γ pathways. The downstream of $p75^{NTR}$ is the recruitment of different adaptors, such as protein BEX3, neurotrophin (NT) receptor interacting factor and neutrophin receptor-interacting MAGE homolog. $p75^{NTR}$ can interact with the Nogo receptor and LINGO-1, and its mobility is influenced by the lipid composition of the plasma membrane. Trk and $p75^{NTR}$ can cross-talk via ARMS (ankyrin-rich membrane spanning). The stoichiometry of receptors and ligands is only conceptual.

of Aβ, itself a potentially neurotoxic protein. Moreover, α_2-macroglobulin protein upregulated in the retina during glaucoma (75) can bind to and neutralize the pro-survival activity of mature NGF. This might explain the paradox whereby NGF is upregulated but unable to mediate survival signals. Moreover, it is likely that the reported pharmacological use of NGF as a therapeutic for glaucoma (76) might be effective because of the massive doses of NGF used and the high frequency of application. Conceivably, high NGF doses might mop all the α_2-macroglobulin protein in the retina. So far, success using NGF in human glaucoma has been reported in Italy, but it would be highly encouraging if these findings were replicated elsewhere. The odds are low, however, because of the poor ability of NGF to cross the human corneal surface when applied topically, the short half-life of the NGF protein, and because most experimental glaucoma models have shown that neurotrophins (including NGF) are effective for only a short time and only when applied at high doses and frequency, or when they are persistently expressed with viral vectors.

HOW CAN WE ACTIVATE TRK PRO-SURVIVAL ACTION AND BYPASS $P75^{NTR}$ PRO-DEATH ACTION?

Given the interplay and actual opposing functions of the two NT receptors, it is also important to consider that in the retina Trk and $p75^{NTR}$ receptors are expressed in different cell types. Simply put, TrkA and TrkB are mainly expressed in RGCs, while TrkC (mainly TrkC.T1) and $p75^{NTR}$ are principally expressed in glia (9, 39, 44, 45, 71).

For that reason, the damaging actions of TrkC.T1, described above, are paracrine (73). Is the presence of $p75^{NTR}$ in glia also deleterious? Interestingly, $p75^{NTR}$ is implicated in the production or secretion of TNF-α (77). It is likely that $p75^{NTR}$ and TrkC.T1 may cooperate in some fashion, since they are co-localized in activated glia. We recently showed that $p75^{NTR}$ and TrkC.T1 cooperate to produce both TNF-α and α_2-macroglobulin (73, 78). For these reasons, it would be desirable to target the "positive" action of Trks while bypassing the "negative" actions of p75.

TARGETING NT RECEPTORS

In animal models of glaucoma the use of NGF, BDNF or NT-3 can exert a protective function for short periods of time (e.g., 2-4 weeks) (61, 62). As discussed above, this can be explained by the poor pharmacokinetics of NTs (79) and the fact that NTs bind to Trk (in neurons) and $p75^{NTR}$ (in glia), thereby activating pro-survival and pro-death signaling. Therefore, agonistic activation of Trk receptors, while excluding p75 activation, could be useful for neuroprotection strategies (23, 80, 81). To this end, our laboratory and others have developed agonists that selectively activate TrkA, TrkC or TrkB, but not $p75^{NTR}$. In addition, we also postulate that p75 antagonists would be beneficial to reduce neurotoxicity.

Broadly speaking, three approaches have been developed. First, there are compounds that activate Trk indirectly (82), for example by acting through G protein-coupled receptors. Second, there are compounds that influence neurotrophin expression or secretion (83). These do not seem appropriate for drug development because the off-target effects are complex. Also, for neuroprotection in the retina, it would be desirable to apply Trk-selective agonists that avoid engaging p75, because Trks and p75 are anatomically segregated in different layers and different cell types, and activation of the p75 receptor can be deleterious to RGCs. As a third alternative, it is possible to develop compounds that activate Trk receptors directly. The first small cyclic peptide structural analogue of NGF (84) was subsequently also reported by others (85-87). The first peptidomimetic of NGF (88) has been used successfully in vivo in chronic animal models of degenerative age-associated memory impairment or glaucoma (9, 89), and in the acute animal model of degenerative optic nerve axotomy (45). This compound is a selective TrkA agonist that does not target p75. An exciting finding was that the TrkA agonist was additive with the protective action of pressure-lowering drugs. This was expected, based on different mechanisms of action, but nonetheless is a key finding because it offers promise to NTG patients.

These findings motivated the design of other derivatives (81, 90, 91), and, more recently, also a series of selective TrkB agonists that were neuroprotective in glaucoma, as well as in optic nerve axotomy models (67). Other promising compounds include agents that potentiate the actions of neurotrophins on Trk receptors (81) and fungal metabolites which are nonselective (92).

HOW HAVE SCIENTISTS STUDIED NEUROPROTECTION IN GLAUCOMA?

Selective TrkA and TrkB agonists can protect RGCs in chronic (glaucoma) and acute (axotomy) RGC neurodegeneration models (9, 45, 67). In these experiments, the use of the natural ligands NGF or BDNF did not protect RGCs. Antagonists of p75 or related neurotoxic pathways are also protective for RGCs, although p75 is expressed in glia (9, 45, 75).

For in vivo neuroprotection studies, scientists use "glaucomatous" animal models such as "artificial hypertension" models or a "spontaneous hypertension" model (15). The "artificial hypertension" animal models are based on the theory of obstruction of the aqueous humor outflow, including the episcleral vein cauterization/ligation (EVC/EVL) model (93, 94), the hypertonic saline injection model (95-97), the laser-induced chronic hypertension model (98, 99), and recently, the injection of microbeads in the anterior chamber in rodents.

The DBA/2J mouse strain is a popular secondary glaucoma model of "spontaneous hypertension" (100-102). MyoC Tyr423His mutations in transgenic and knockout mice also display some of the characteristics of glaucoma (38, 103, 104). Moreover, deficiencies in the glutamate transporters GLAST-1 or EAAC1, and the expression of mutated optineurin (E50K) in transgenic mice led to RGC death and degeneration of axons in the optic nerve, without IOP elevation (96, 105), in models of NTG. None of these models recapitulates all of the features of human glaucoma, and it is important to remember that they are simplified, reductionist models.

CRITERIA FOR FOLLOWING NEUROPROTECTIVE STRATEGIES IN GLAUCOMA

Neuroprotective drugs must comply with the following conditions: the molecular target is present in the retina or the optic nerve; the drug candidate is selective for the target; an effective concentration can reach the retina or optic nerve; the mechanism of action is to slow down or reverse optic nerve injury or to protect neurons from injury or to reduce neurotoxicity; the drug causes no off-target effects (22, 106).

WHAT ARE THE LATEST NEUROPROTECTION STRATEGIES FOR GLAUCOMA?

As we have discussed, the potential for the clinical use of neuroprotective strategies in patients with glaucoma has been studied (107, 108). Hundreds of agents have been investigated for neuroprotection in animal models of glaucoma, including anti-excitotoxic agents (109), free radical scavengers (110), antiapoptotic agents (111), anti-inflammatory factors (12) and neurotrophic factors (112). However, results are mixed, and the translation of neuroprotective agents in humans has lagged.

Neuroprotection has not been fruitful in other conditions such as Alzheimer's disease, Parkinson's disease, some forms of pain and amyotrophic lateral sclerosis (ALS) either (23, 80). For example, in spite of poor performance in cognitive disorders, memantine was tested in phase III clinical trials in open-angle glaucoma patients. The effects of memantine could not be distinguished from the placebo-treated group. Therefore, the *standard* treatment and the *only* proven effective methods for patients with glaucoma remain IOP-lowering strategies (6).

We hope that the failure of memantine in glaucoma will not be the end of neuroprotection. Without a doubt, neuroprotective strategies offer promise as therapeutic methods. Neuroprotectants would not replace IOP-lowering drugs, but rather would be used as an adjuvant therapy to ameliorate the progressive loss of visual function.

Targeting neurotrophin receptors with ligands that activate survival pathways or inhibit death pathways is an alternative worth pursuing. Other interdisciplinary therapeutic methods such as stem cell-based therapies, antiapoptotic signaling agents, gene therapy and artificial vision techniques could also offer alternatives to glaucoma treatment.

Some of the potential agents will fulfill the key requirements in the treatment of this irreversible disorder, which has proven to be beyond the capacity of IOP-lowering drugs or surgery. It is to be expected that receptor-selective agents, biopharmaceuticals (e.g., monoclonal antibodies), as well as immunomodulatory agents, will be available for the treatment of glaucoma patients, which will complement the currently available armamentarium of disease-modifying drugs.

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DISCLOSURES

The authors state no conflicts of interest.

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