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Neuroprotective Factors of the Retina and Their Role in Promoting Survival of Retinal Ganglion Cells: A Review

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Abstract
Retinal ganglion cells (RGCs) play a crucial role in the visual pathway. As their axons form the optic nerve, apoptosis of these cells causes neurodegenerative vision loss. RGC death could be triggered by increased intraocular pressure, advanced glycation end products, or mitochondrial dysfunction. In this review, we summarize the role of some neuroprotective factors in RGC injury: ciliary neurotrophic factor (CNTF), nerve growth factor (NGF), brain-derived neurotrophic factor, vascular endothelial growth factor, pigment epithelium-derived factor, glial cell line-derived neurotrophic factor, and Norrin. Each, in their own unique way, prevents RGC damage caused by glaucoma, ocular hypertension, ischemic neuropathy, and even oxygen-induced retinopathy. These factors are produced mainly by neurons, leukocytes, glial cells, and epithelial cells. Neuroprotective factors act via various signaling pathways, including JAK/STAT, MAPK, TrkA, and TrkB, which promotes RGC survival. Many attempts have been made to develop therapeutic strategies using these factors. There are ongoing clinical trials with CNTF and NGF, but they have not yet been accepted for clinical use.

Introduction

The Anatomy of the Retina

The retina is a complex structure that receives visual information. It consists of 10 layers, 9 inner layers are neural, and the outermost layer is the retinal pigment epithelium (RPE) [1]. In addition to light absorption, the RPE plays a role in nourishing the neuroretina, maintaining ionic equilibrium, and retinaldehyde metabolism [2]. The retina's neural part is composed of 5 major neuron types: bipolar cells, ganglion cells, horizontal cells, amacrine cells, and photoreceptors, which form a highly ordered 9-layer structure [1, 3]. Recently, novel approaches to the structural organization of the neuroretina of the neuroretina have been described. A simplified division distinguishes 3 layers of neuron bodies containing nuclei and 2 layers of synaptic connections between them, mak-

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ing 5 layers in total [4]. Each type of retinal cell comprises a mosaic-like structure that provides a regular distribution throughout the retina [5]. Signal transduction in the retina begins with the isomerization of 11-cis retinal bounded to one of the visual pigments – rhodopsin for rods and cone opsin for cones. Next, the signal from the photoreceptors reaches the bipolar cells through glutamate-mediated synapses. This process is controlled by the horizontal cells. Bipolar cells convey the signal to the retinal ganglion cells (RGCs) [6–8]. The anatomy of the neural retina and receptors of the RGCs is shown in Figure 1.

Retinal Ganglion Cells

RGCs form the innermost layer of the neural retina and are the last cells of the neural net to receive visual stimulus within the eye. Their axons form the optic nerve, which conducts the visual information as impulses to the brain [6]. The electrical stimulus passed by the RGCs to the visual cortex consolidates the modifications made by previous neurons of the retina [9]. Therefore, RGCs play a vital and indispensable role in the process of vision and their injury can lead to irreversible blindness, as seen in advanced glaucoma [10]. Neuroprotection of these cells is a broadly studied therapy option that could eventually stop the development of disease [11].

Mechanisms Involved in Retinal Ganglion Cell Damage

As described above, the retina is a structure composed of neuronal cells which are prone to degeneration due to injury, aging, diabetes, and ocular hypertension [12, 13]. The mechanisms involved in RGC protection are described in Figure 1. Neurotrophic factors contribute to the survival of RGCs in case of damage due to their antiapoptotic activity. Neurons that do not receive adequate signals undergo apoptosis [14]. It has been shown that advanced glycation end products, which are associated with aging and diabetes, induce activation of caspase 3, one of the executioner caspases actives in apoptosis, in the retinal explant cells [15, 16]. However, the presence of the active forms of caspases 3 and 9 in retinal cells exposed to high glucose levels incubated with neurotrophic factors (e.g., brain-derived neurotrophic factor [BDNF]) was significantly lower than in the control group [17]. Elevated intraocular pressure (IOP), which is a relevant risk factor in glaucoma pathogenesis, leads to the expression of high-mobility group box 1 (HMGB1) protein and then leads to inflammasome activation which triggers further inflammation [18]. Increased IOP also induces phosphorylation of antiapoptotic cytoplasmic protein 14-3-3. Phosphorylation of 14-3-3 enables the dephosphorylation and consequently the activation of the proapoptotic protein Bcl-2 associated agonist of cell death (BAD) [19]. Another study showed that elevated IOP enhances Bax expression, which is also a proapoptotic factor [20]. Apoptosis in glaucoma and diabetic retinopathy can be induced directly by inflammatory cytokines such as tumor necrosis factor-alpha (TNFα), as well as membrane-bound Fas-ligand (FasL) [21–23]. Interestingly, soluble FasL appears to have a neuroprotective activity [22]. It is worth noting that expression of FasL and other proapoptotic factors such as active caspases 3 and 8 was upregulated in the retina of diabetic patients compared with healthy individuals and no difference was observed in the expression of antiapoptotic markers: B-cell lymphoma-extra large (Bcl-xL), FLICE-like inhibitory protein (FLIP), and cyclooxygenase-2 (COX2) [24]. Also, mitochondrial dysfunction might play a role in RGC death [25]. Mutations in mitochondrial DNA (mtDNA) caused by increased IOP lead to the progressive loss of RGCs. This damage includes flaws in the electron transport chain and consequently alteration in the reactive oxygen species (ROS) levels, leading to further mtDNA damage. Mutant mitochondria also do not provide enough adenosine triphosphate production. Ultimately, even when the IOP lowers, mitochondrial derangement leads to the apoptosis of RGCs [26, 27]. Aging also leads to elevated levels of ROS, which is one of the major correlations of gradual vision impairment in the elderly [28]. Eventually, RGCs are lost physiologically with increasing age [29].

Aim of the Review

A few proteins have been shown to demonstrate neuroprotective properties in response to retina damage. This review summarizes the up-to-date knowledge about their function in protecting RGCs from degeneration. Also, we have outlined the recent experimental and clinical trials which explore the therapeutic possibilities of neuroprotective factors in acute neuropathies such as optic nerve crush and in chronic neuropathies such as glaucoma.

Proteins with Neuroprotective Properties

Ciliary Neurotrophic Factor

Ciliary neurotrophic factor (CNTF) is a neuropoietic cytokine that belongs to the IL-6 family. It binds to a gp130 receptor to activate the JAK/STAT and MAPK

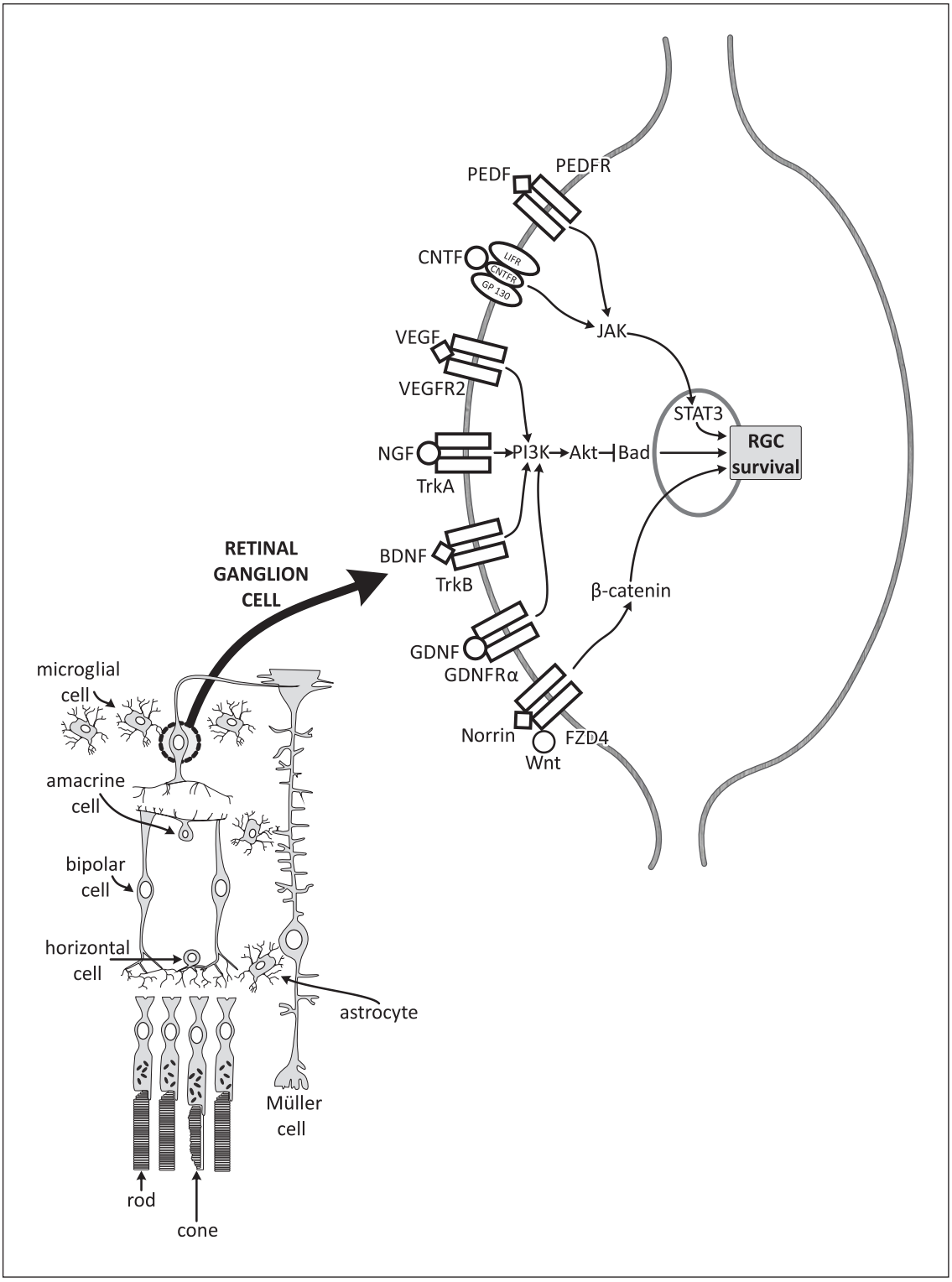

Fig. 1. The anatomy of the neural retina and receptors of the RGCs. The pathways are activated by neuroprotective factors.

pathways [30]. These signaling pathways regulate gene expression to stimulate neuron regeneration in mice and zebra fish [31, 32]. In the eye, CNTF exerts a neuroprotective effect on photoreceptors and the RGCs by stimulating regeneration [33]. It was also shown that CNTF deprivation does not cause neurodegeneration in the retina [34]. However, CNTF administration can significantly increase the survival of retinal cells [35]. Many studies have been conducted to define the best way of CNTF delivery to the retina.

Intravitreal injection of CNTF in a murine model of nonarteritic anterior ischemic optic neuropathy revealed a significant increase in the survival rate of RGCs compared with the control group [36]. An increase in the survival of RGCs was also noted when intravitreal injection of CNTF was combined with cyclic adenosine monophosphate analog [37]. Two administration routes were compared in an in vitro study of RGCs with H_2O_2-induced injury: (i) using lentiviral vectors carrying the CNTF gene and (ii) adding the protein to the culture medium. Although a neuroprotective effect was observed in both groups, there was no significant difference in the survival of RGCs between the 2 methods [35].

Adeno-associated viral vector (AAV)-mediated CNTF gene transfer has been proven to support axon regeneration of RGCs after optic nerve crush [38, 39]. However, Hellström et al. [40] pointed out that the effect of CNTF administration via adeno-associated viral vector is delayed because of the time needed to start gene expression. To maintain the therapeutic effect during the delay, a combined genetic and pharmacological treatment (the administration of recombinant CNTF with cyclic adenosine monophosphate analog) was proposed which turned out to be very effective in protecting the RGCs after nervous tissue trauma in rats [40].

Neural stem cells can be genetically modified to produce more CNTF and can then be grafted into the vitreous body to exert a neuroprotective effect as shown in a mouse model after optic nerve crush [41]. When neural stem cells that produce glial cell line-derived neurotrophic factor (GDNF) were added to the CNTF therapy, the proteins had a synergic effect in the protection of RGCs [42].

Another method of modulating CNTF expression is through the inhibition of the purinergic receptor P2X7 (P2X7R) [43]. The P2X7R is an ionotropic receptor activated by extracellular adenosine triphosphate, which promotes the synthesis of various pro-inflammatory mediators that support neuroinflammation which later leads to neurodegeneration. The P2X7R can be found on microglial cells, astrocytes, and neurons throughout the central nervous system including the retina, and also in other structures of the globe such as the cornea, lens cells, etc. [43, 44]. Antagonizing P2X7R weakens the inflammatory response and leads to neuroprotection [43, 45–47]. Recently, it was shown that chronic application of eye drops containing P2XR7 antagonist in mice with glaucoma decreased the number of activated microglia and prevented the loss of RGCs [46]. Inhibiting P2X7R has been shown to increase the levels of CNTF in neurons. However, delivering to mice Brilliant Blue G, the well-known P2X7R antagonists, exerts no neurogenic effect, despite increasing pro-neurogenic CNTF due to the simultaneous inducement of counteracting growth factors [48].

Nerve Growth Factor

Nerve growth factor (NGF) is a neurotrophic factor secreted by multiple cells: neurons, Schwann cells, and oligodendrocytes of the nervous tissue; mast cells, T cells, and macrophages of the immune system; keratinocytes, melanocytes, and fibroblasts of the skin; and even by smooth muscle cells. Its functions include regulating neurogenesis and apoptosis, promoting neuron plasticity, modulating a neuron's response to heat and pain, and participating in the process of neuroinflammation with nociceptor activation [49]. There are 2 NGF receptors in the retina: the RGCs express the transmembrane tyrosine receptor kinase A (TrkA), while glial cells express the p75 neurotrophin receptor ($p75^{NTR}$). NGF, like BDNF, is produced not only in the retina but also in the brain, from where it is transported via the neurons of the optic disc. Disturbance in this pathway leads to altered NGF levels in the retina [50]. NGF can be blocked by α2-Macroglobulin, which precludes NGF interaction with its receptor. A lack of NGF trophic function leads to a decrease in the survival rate of retinal cells [51].

Attempts to prevent RGC death in glaucoma by NGF administration did not meet expected outcomes, probably due to NGF activating the receptors of the opposite action – TrkA and $p75^{NTR}$ [52]. Mesentier-Louro et al. [53] studied the effect of optic nerve crush on the upregulation of NGF, proNGF, and $p75^{NTR}$. It was proposed that while NGF exerts a neuroprotective action by activating TrkA, proNGF activates $p75^{NTR}$ to promote apoptosis, with the overall result being RGC degeneration [53]. Therefore, effective treatment should include a drug that selectively activates the neuroprotective TrkA or inhibits the proapoptotic $p75^{NTR}$ [52, 54]. On the other hand, Guo et al. [55] showed that topical administration of recombinant human NGF (rh-NGF) does exert significant neuro-

protection in animal optic neuropathy models. The described mechanism involves inhibition of the secondary neurodegenerative processes [55].

Brain-Derived Neurotrophic Factor

BDNF is a neurotrophin produced by neurons in the retina, such as RGCs, amacrine cells, astrocytes, retinal glial cells (Müller cells), and photoreceptors [56, 57]. BDNF can also be transported between the brain and the retina via the optic nerve [58, 59]. Its primary functions in the nervous system include controlling neural development, modulating synaptogenesis, and neuroprotection [60]. In the retina, BDNF plays a vital role in vision signaling development by regulating laminar refinement in the dendrites of RGCs, which leads to the proper formation of the retinal structure [61]. In mature individuals, endogenous BDNF exerts neuroprotective effects on RGCs by protecting dendritic fields and reducing vision loss after ocular hypertension-induced injury, which was observed in animal models of ocular hypertension and glaucoma [58, 62]. Another function of BDNF is protection of the retina cells from injuries caused by hypoxia and glucose deprivation [63].

Tropomyosin receptor kinase B (TrkB), the BDNF receptor [64], may also be activated by specific immunoglobulins. Administration of mouse monoclonal antibodies, which act as TrkB exogenous selective agonists, promotes antiapoptotic activity [65]. The Src homology region 2-containing protein tyrosine phosphatase 2 (Shp2) has been identified as playing a role in BDNF-TrkB signaling. Shp2-mediated TrkB dephosphorylation inhibits the signaling pathway and thus leads to decreased survival of the RGCs. Modulating Shp2 activity appears to be a new target in experimental glaucoma therapy [66].

Similar to CNTF, BDNF expression may also be influenced by purinergic receptor signaling. P2X7R, mentioned above, has been shown to influence BDNF action: antagonizing P2X7R leads to TrkB activation [67]. BDNF expression can also be modulated by purinergic receptors that belong to the P1 family of metabotropic receptors activated by extracellular adenosine. There is a complex crosstalk between the P1A1 receptors, the P1A2A receptors, interleukin-6 expression, and BDNF expression, which is not fully understood [68]. Nevertheless, antagonism of the P1A1 and P1A2A receptors is considered to be a potential future therapeutic option for neurodegenerative diseases of the central nervous system [44, 69].

BDNF has been used therapeutically in animal models of glaucoma. However, intravitreal administration of a recombinant protein has a time-limited effect due to the downregulation of TrkB that follows [70–72]. To counteract this effect, a novel gene therapy transferring both the BDNF and the TrkB gene has been proposed and was proven to promote long-term survival of the RGCs in a rodent model of optic nerve injury [73].

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is a family of proangiogenic factors that includes 7 proteins: VEGF A, B, C, D, E, F, and placental growth factor. The most widely distributed in human tissue is VEGF A, which is commonly referred to simply as "VEGF" [74]. In the eye, it is secreted by multiple cells, such as cells of the vascular and RPE, Müller cells, astrocytes, and RGCs. VEGF binds to VEGF receptors 1 (VEGFR-1) and 2 (VEGFR-2) [75]. The primary VEGF functions include promotion of angiogenesis, vasodilation, and increasing vascular permeability [76]. It also plays a role in the pathomechanism of ocular retinopathies, e.g., exudative age-related macular degeneration and diabetic macular edema [75]. However, VEGF exhibits neuroprotective properties. It was shown that VEGF-A binding to VEGFR-2 and activation of the PI3-K/ACT pathway was necessary to promote the survival of the RGCs. This action was not only neuroprotective but also sufficient for glaucoma prevention [77]. There are 2 isoforms of VEGF-A (VEGF-A165a and VEGF-A165b). VEGF-A165b is of greater importance in neuroprotection and may be useful in treating neuropathies, but it also exhibits angiogenic activity [78]. Therefore, the administration of VEGF in ocular disorders for its neuroprotective effect is disputable due to the high chance of vascular adverse effects. In vitro studies showed that non-inflammatory VEGF121 modified to be bound to a cell membrane, thus exerting an autocrine effect only, was beneficial for the survival of RGCs and also lacked the ability to bind to other cells [79]. Surprisingly, the administration of ranibizumab, a humanized antibody that binds VEGF-A after optic nerve injury, attenuates the loss of RGCs. A negative correlation was shown between VEGF concentration in the aqueous humor, peripheral blood, and the number of surviving cells [80].

Pigment Epithelium-Derived Factor

Pigment epithelium-derived factor (PEDF) in the retina is secreted by the Müller cells and exhibits antiangiogenic and neuroprotective activity. It can prevent damage to RGCs and stimulate axogenesis [81–83]. PEDF inhibition has been shown to decrease the survival of RGCs in vitro [84, 85]. Several mechanisms of action have been proposed: caspase 2 suppression, upregulation of the un-

coupling of protein 2, prevention of mitochondrial dysfunction, and activation of the STAT3 pathway [86–89]. It was shown that increased (IOP) leads to the upregulation of PEDF and its receptor – PEDF-R, thus inhibiting apoptosis of RGCs [90]. Also, the method of administration may have an impact on effectiveness. Vigneswara et al. [91] investigated the difference between daily eye drop delivery and weekly intravitreal injections in rats after optic nerve crush and showed the greater effectiveness of daily eye drop delivery for the survival of RGCs. Gene therapy through lentiviral vectors has also been proven to attenuate the apoptosis of RGCs in ocular hypertension models [92].

Glial Cell Line-Derived Neurotrophic Factor

Four proteins belonging to the glial cell line-derived neurotrophic factor (GDNF) family of ligands have been described: GDNF, artemin, neurturin, and persephin. They play a vital role in the development and function of the nervous system, in spermatogenesis, and in renal growth [93, 94]. Many studies focused on the role of GDNF family of ligands in the retina, proving their neuroprotective effect on photoreceptors and RGCs [95, 96]. Post-injury apoptosis of RGCs may be promoted by extracellular glutamate, whereas GDNF and neurturin prevent the proapoptotic cascade by upregulating the glutamate transporter levels which leads to the uptake of the glutamate by retinal cells [97]. In the rodent models of glaucoma, administration of GDNF-loaded microspheres by intravitreal injections resulted in increased density of the RGCs [98], increased axon survival, and lowered proinflammatory glial cell activation [99]. After adding vitamin E to the microsphere structure, an additive effect can be observed due to the vitamin's antioxidant and antiproliferative properties [100].

Norrin

Norrin is a protein constitutively expressed by the Müller cells in the retina. It has functional similarity to growth factors, and its reported functions include angiogenesis stimulation and neuroprotection [101]. Norrin binds to the Frizzled-4 (FZD4) receptors to activate the Wnt/β-catenin signaling pathway, which promotes cell survival. It has been proven that inhibiting this signaling pathway (through dickkopf-1, a Wnt/β-catenin inhibitor) suppresses the action of Norrin [102, 103]. Another proposed mechanism of neuroprotection involves the leukemia inhibitory factor (LIF), which is necessary for the gliosis of Müller cells – a reaction of neural cells that contributes to the maintenance of retinal homeostasis in physiological and pathological states [104]. After excitotoxic damage, Norrin induces LIF expression in retinal neurons, which in turn stimulates Müller cells to secrete protective factors – endothelin 2 (ET-2) and fibroblast growth factor 2 (FGF2) [105].

The neuroprotective effects of Norrin were shown in both acute and chronic neuropathies. After protease-mediated injury of RGCs, the protein acts via the Wnt/β-catenin signaling pathway to increase the survival of RGCs [106]. In a mouse model of glaucoma, genetically modified individuals with overexpression of the Norrin gene showed greater survival of RGCs [107].

Norrin has also been studied in a rodent model of oxygen-induced retinopathy. It was shown that intravitreal injections of Norrin correlated with a higher density of RGCs and a thicker nerve fiber layer [108].

Eye Disease Therapies Based on Neuroprotective Factors in Clinical Trials

As of today, little is known about the translation of neuroprotective factor therapies into clinical use. New treatment strategies are researched for diseases primarily caused by the degeneration of RGCs such as glaucoma, and other ophthalmic diseases such as macular degeneration, retinitis pigmentosa, ischemic optic neuropathy, macular telangiectasia, and cystoid macular edema (Table 1). The only tested CNTF-based therapy for the abovementioned diseases, with the exception of cystoid macular edema, is the NT-501 encapsulated cell implant-based therapy. NT-501 is an implant containing immortal cells, genetically modified to express CNTF, embedded on a polymer scaffold. It is inserted into the eye globe through the inferotemporal quadrant of the sclera and affixed with a single suture during a 15-min procedure. Although many studies on phase 2 were conducted on this implant, no further phase 3 trials have been registered at https://clinicaltrials.gov/ [109–113]. Currently, an extension study is conducted among patients with Macular Telangiectasia Type 2, an idiopathic disease considered as primarily neurodegenerative [114]. This extension study was justified by the positive outcome of previous investigations (NCT03071965) [113]. Another therapy, with topical administration of human recombinant NGF (rh-NGF), appears to be in the early stage of introduction to clinical use [115]. Patients receive eye drops which penetrate the conjunctival sac to reach the inner part of the globe. This approach was proven as safe and then tested on neurotrophic keratitis, which is not associated with

Table 1. Clinical trials using neuroprotective factor-based therapies registered at clinicaltrials.gov (up to June 2020)

Factor	Group of patients	Clinicaltrials.Gov identifier	Intervention	Phase of clinical trial	Year of study start	Results
CNTF	Glaucoma	NCT01408472	NT-501 Encapsulated cell therapy	1	2011	Not published
		NCT02862938		2	2016	
	Retinitis pigmentosa	NCT00063765		1	2003	Positive safety profile [100]
	Retinitis pigmentosa (early stage)	NCT00447980		2	2007	Not significant changes in visual field and visual acuity [100, 102]
	Retinitis pigmentosa (late stage)	NCT00447993		2	2007	Not significant changes in visual field and visual acuity except decrease in vision sensivity in high-dose treated patients [102]
	Macular degeneration and geographic atrophy	NCT00447954		2	2007	Structural and functional improvements in retina [99, 100]
	Ischemic optic neuropathy	NCT01411657		1	2011	Not published
	Macular telangiectasia type 2	NCT01327911		1	2011	Positive safety profile [101]
		NCT01949324		2	2003	Slower progression of retinal degradation [103]
		NCT03071965		2 (extension study)	2017	Not published
NGF	Glaucoma	NCT02855450	Topical administration of rhNGF drops	1	2016	Not published
	Retinitis pigmentosa	NCT02110225		2	2014	Results published on https://clinicaltrials.gov/without analysis
	Retinitis pigmentosa and cystoid macular edema	NCT02609165		2	2015	Not published
	Healthy volunteers	NCT01744704		1	2012	Positive safety profile [105]

CNTF, ciliary neurotrophic factor; NGF, nerve growth factor; rhNGF, recombinant human nerve growth factor.

damage to RGCs but with impairment of the ophthalmic branch of the trigeminal nerve innervating the cornea [115, 116]. The phase 2 study suggested that rh-NGF could be effective in neurotrophic keratitis treatment [117]. Drugs acting as a decoy to VEGF are currently tested as an intravitreal therapy mainly for macular degeneration patients [118, 119]. The collective inhibitor of VEGF and PDGF administered intravitreally was also tested, and results revealed that the combination of both leads to relatively higher visual activity compared with monotherapy [120]. In some studies, ranibizumab, a VEGF-A antibody, was combined with novel drugs such as pazopanib eye drops (a VEGFR tyrosine kinase inhibitor), but no significant improvement was observed compared to ranibizumab only [121]. Altogether, a significant number of studies are investigating VEGF-related agents, based on the number of searches at https://clinicaltrials.gov/; however, all of them focus on inhibiting neovascularization. No studies on neuroprotective therapy based on VEGF were found. As for P2X7R, even though preclinical data shows promise, no clinical trials targeting this receptor in therapy of ophthalmic diseases have been registered.

However, neurotrophic factors are not the only agents presenting neuroprotective properties. Citicoline (cytidine 5′-diphosphocholine) is currently used as a dietary supplement as it has been proven to mitigate symptoms of neurological diseases such as Alzheimer's disease. Experimental data show that citicoline exhibits neuroprotective, neurorestorative, and regenerative activity in retinal cells in vitro and in animal models. Also, clinical trials have confirmed positive outcomes from the use of citicoline in patients with glaucoma [122]. Some reports indicate that simvastatin exhibits neuroprotective properties by inhibiting stress-related intracellular pathways in microglia and astrocytes in animal models. This action

results in attenuated inflammation in the retina, which may protect RGCs from death [123, 124]. The coenzyme Q appears to have neuroprotective properties presumably by acting as a ROS scavenger [125, 126]. Overall, this brief overview of a few examples suggests that well-known substances might be useful in the treatment of damage to RGCs and this area needs further study.

Conclusion

Neurodegeneration is a pathomechanism that underlies many ophthalmic diseases, such as glaucoma, diabetic retinopathy, age-related macular degeneration, and retinal ischemia-reperfusion injury. As of today, modulating the expression of neuroprotective factors is not the treatment option for ophthalmology patients. However, with many promising results from preclinical studies, it may become a therapy option for some diseases in the future. It is worth remembering that neuroprotection can also be stimulated by substances other than neuroprotective factors, such as P2X7R antagonists, citicoline, statins, coenzyme Q, and others. However, their detailed description exceeds the scope of this review. Another important matter for researchers is to create a fully reliable model of injury to RGCs which will enable a better understanding of the efficacy of neuroprotective factors and their full potential. This review summarizes the most significant results and covers the basic foundation knowledge necessary to understand the subject. It is essential for ophthalmology specialists to stay up to date with recent findings, such as the introduction of neuroprotective factors. However, this vast subject still needs further investigation which might provide clinicians with the information needed to treat patients with therapies based on neuroprotective factors. Further studies are crucial to fully understand the impact of these proteins on RGCs.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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