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Review

Novel frontiers in neuroprotective therapies in glaucoma: Molecular and clinical aspects

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ABSTRACT

In the last years, neuroprotective therapies have attracted the researcher interests as modern and challenging approach for the treatment of neurodegenerative diseases, aimed at protecting the nervous system from injuries. Glaucoma is a neurodegenerative disease characterized by progressive excavation of the optic nerve head, retinal axonal injury and corresponding vision loss that affects millions of people on a global scale. The molecular basis of the pathology is largely uncharacterized yet, and the therapeutic approaches available do not change the natural course of the disease. Therefore, in accordance with the therapeutic regimens proposed for other neurodegenerative diseases, a modern strategy to treat glaucoma includes prescription of drugs with neuroprotective activities. With respect to this, several preclinical and clinical investigations on a plethora of different drugs are currently ongoing. In this review, first, the conceptualization of the rationale for the adoption of neuroprotective strategies for retina is summarized. Second, the molecular aspects highlighting glaucoma as a neurodegenerative disease are reported. In conclusion, the molecular and pharmacological properties of most promising direct neuroprotective drugs used to delay glaucoma progression are examined, including: neurotrophic factors, NMDA receptor antagonists, the α2-adrenergic agonist, brimonidine, calcium channel blockers, antioxidant agents, nicotinamide and statins.

1. Introduction

Neurodegeneration is characterized by a progressive loss of neurons and their processes (axons, dendrites, synapses) in defined areas of the nervous system and a concomitant impairment of neuronal function. The most prevalent neurodegenerative diseases such as Alzheimer's disease (AD), glaucoma, age-related macular degeneration (AMD), Parkinson's disease (PD), and others, develop in selected neuroanatomical areas and in different neuron subgroups of highly specialized tissues, from the eye retina to brain regions. Despite their divergent clinical manifestations, neurodegenerative disorders are multifactorial and often share common molecular mechanisms at the basis of disease onset, such as abnormal protein aggregation, mitochondrial dysfunction, oxidative stress and inflammation (Angeloni et al., 2022; Baldassarro et al., 2022; Tarozzi and Angeloni, 2023). Over the last years, the main paradigm for the cure of neurodegeneration has been "one drug, one activity, one disease", and a great number of preclinical and clinical treatments are currently investigated. However, most available therapeutic options are symptomatic, with approved drugs having limited clinical impact on disease progression (García and Bustos, 2018; Peña-Bautista et al., 2020). Hence, there is an urgent need of disease-modifying therapies to prevent, slow and even stop the progression of neurodegeneration. The attention of researchers is now focused on the discovery of multi-targeted compounds, in which the same molecule can exert its effects by targeting different molecular pathways. The definition of neuroprotection is wide and complex, and it

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refers to the mechanisms and strategies aimed at protecting the nervous system from injury and damage. Neuroprotective strategies support neuronal survival and, in the case of ongoing neurodegenerative insult, promote the maintenance of neuron structure and function, leading to a reduction in the rate of neuronal loss over time. Therefore, efficacious neuroprotective therapies are expected to gain disease modifying properties, even though, to date no directly neuroprotective therapies have been approved by regulatory agencies (Villoslada and Steinman, 2020; Yanamadala and Friedlander, 2010). (see Figs. 1 and 2).

1.1. Neuroprotection in retina

Retinal neurodegenerative diseases such as age-related macular degeneration, demyelinating and hereditary optic neuropathies, glaucoma, diabetic retinopathy and retinitis pigmentosa are the most common disorders that cause progressive and incurable loss of vision (Danesh-Meyer and Levin, 2009; Kaur and Singh, 2021). The complexity and unique architecture of retina renders it vulnerable to multiple pathological insults (Usategui-Martin and Fernandez-Bueno, 2021). Clinical manifestations and etiology, spanning from genetic mutations to various stressful conditions (*i.e.,* high level of glucose in blood and mechanical stress due to enhancement of intraocular pressure) and aging, are quite different, depending on the single pathology. Nevertheless, they reveal some common features at cellular and molecular level, such as inflammation determined by activation of glia, oxidative stress response and progressive cell death of retinal ganglion cells (RGCs) which are the unique output neurons of the retina (Cuenca et al., 2014). RGCs cannot spontaneously regenerate axon, and, as a consequence, their loss results in permanent vision reduction and blindness (Oliveira-Valença et al., 2020). Retina neurodegeneration is usually divided into four phases: 1) the morphology of the retina appears normal, but at molecular level alterations are present; 2) stressful conditions lead to progressive cell death and activation of glia; 3) an extensive neuronal cell death and microglia activation occur; 4) retina architecture is overturned with invasion by blood vessels, hypertrophy of glia cells and RGCs death (Cuenca et al., 2014, p. 201). These progressive stages of dysfunction lead to visual blindness that becomes irreversible in later phases (Gagliardi et al., 2019). As a matter of fact, early-acting therapies are expected to change the disease course of pathology. Retinal neuroprotection represents the next frontier in ophthalmic diseases and for some pathologies (*e.g.*, age-related macular degeneration, inherited retinal dystrophies and macular telangiectasia type 2), neuroprotective strategies are in clinical trials and an increasing number of preclinical studies are published (Levin et al., 2022; Schmetterer et al., 2023; Wubben et al., 2019). Nevertheless, key aspects that render hard to design effective neuroprotective strategies, spanning from molecular to clinical troubleshooting, include: the lack of complete understanding of molecular basis of diseases, the anatomical and tissue complexity of visual system, the time at which patients are enrolled in clinical trials, and the absence of valid endpoints (Levin et al., 2022; Weinreb and Levin, 1999). The progress of investigations to determine the *primum movens* of neurodegeneration and the exact mechanism leading to primary neuronal and/or glia dysfunction is crucial. Therefore, a deeper understanding of the common mechanisms among different neurodegenerative disorders is mandatory. Of note, although the pathophysiology of neurodegenerative diseases affecting eye and brain differs, they show biological commonalties, such as the activation of inflammatory and stress response, and misfolded protein accumulation (Sbardella et al., 2021; Tundo et al., 2021, 2020, p. 20,123; Usategui-Martin and Fernandez-Bueno, 2021). Additionally, in some cases, specific links have been identified, as for mild atrophy of RGCs cells in AD and mild cognitive impairment in glaucoma (Ashok et al., 2020) (see Box. 1). Hence, preclinical studies support the notion that various classes of neuroprotective therapies (*i.e.,* antioxidants, neurotrophic factors, apoptosis and kinase inhibitors, and modulators of ubiquitin-proteasome system) could show similar efficacy in the case of brain and eye neurodegeneration (Pietrucha-Dutczak et al., 2018; Sbardella et al., 2020a; Tundo et al., 2023). A further element of complexity is represented by the fact that RGCs are highly divergent, and their precise physiology is partially unknown. In fact, there is poorly knowledge concerning which specific cell type is fundamental to preserve visual integrity and how different populations respond to the neurodegenerative insult. Moreover, animal and human visual systems differ in term of anatomy, physiology and disease manifestations, making it hard the identification of the correct animal model for testing neuroprotective strategies (Sanes and Masland, 2015; Trenholm and

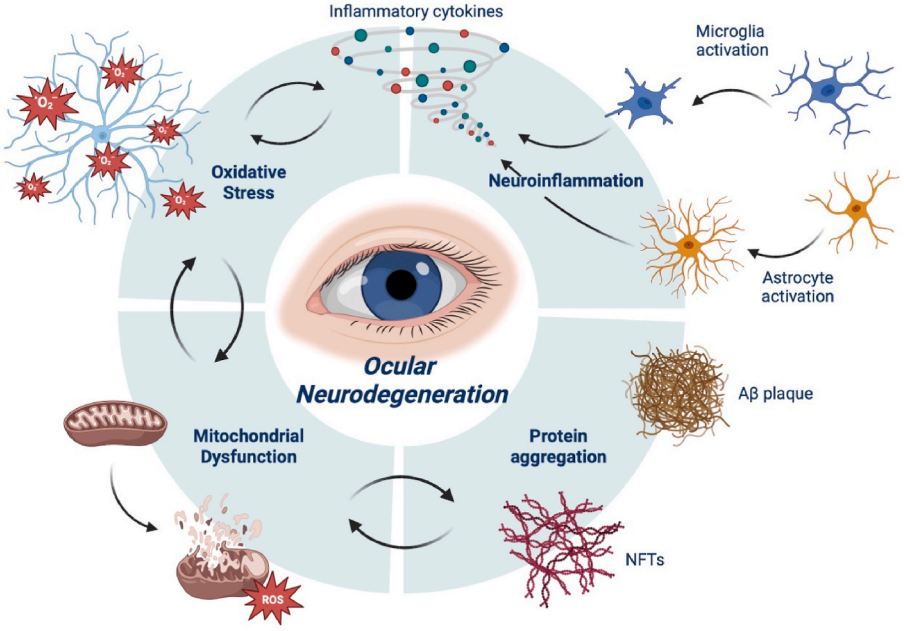

Fig. 1. Mechanisms of neurodegeneration in the retina. The degeneration of neurons in the eye can be triggered by several events, such as mitochondrial dysfunction, oxidative stress, inflammation and protein aggregation. All these events are strictly interconnected, and they can all participate in glaucoma pathogenesis.

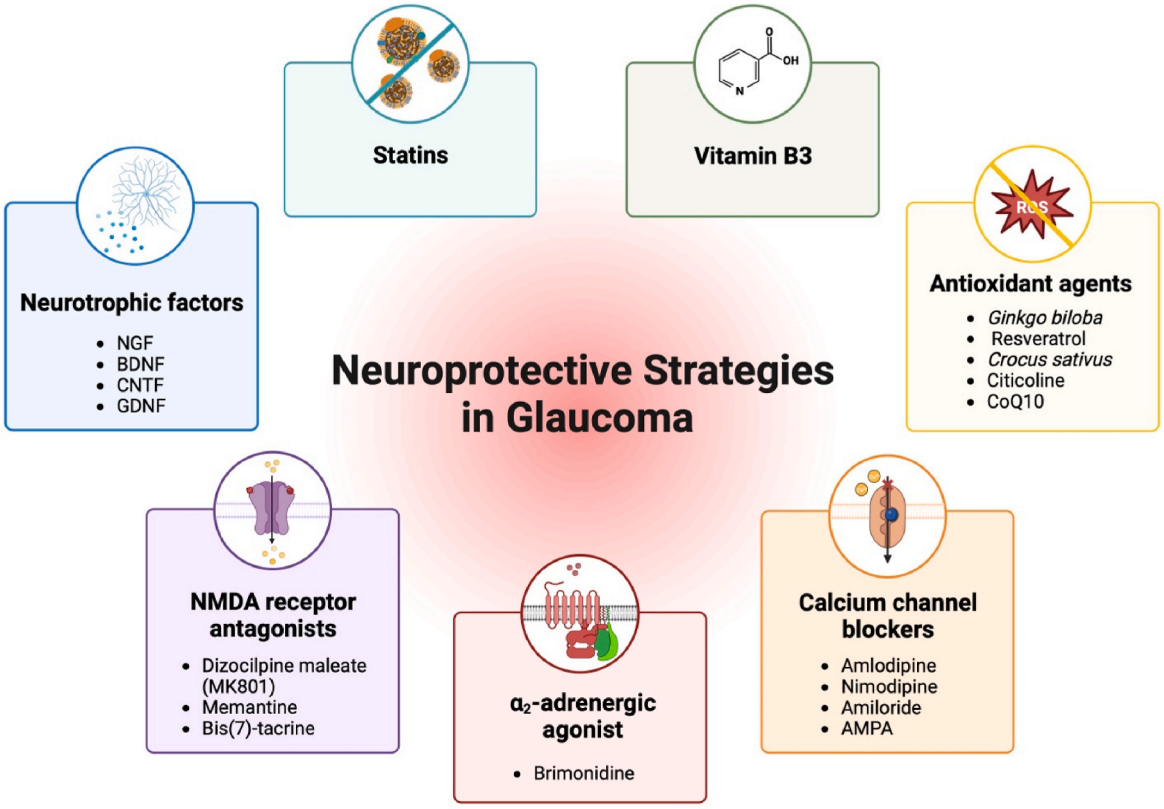

Fig. 2. Neuroprotective agents in glaucoma. Strategies that aim at preventing the degeneration of retinal neurons are classified as direct neuroprotectors. For the treatment of glaucoma, they include neurotrophic factors, NMDA receptor antagonists, alpha2-adrenergic agonists, calcium channel blockers, antioxidant agents, vitamin B3 and statins. Except for the alpha2-adrenergic agonist, brimonidine, all of them show neuroprotective activity without affecting the IOP. Thus, neuroprotectants could be used in combination with IOP-lowering therapies (pharmacological or surgical) to effectively slow down the progression of the disease.

Krishnaswamy, 2020). Nevertheless, with the identification of novel targets and new neuroprotective agents to test, the number of clinical trials in ophthalmology has exponentially increased. However, outcomes are in general below researchers' expectations. The failure of neuroprotection trials could be related to patients' selection issues. To be effective, by definition, neuroprotective strategies should be administrated at an early stage of disease. However, the diagnosis is often belated and patients are enrolled in later phases, when the neuronal function is compromised and the chances that a neuroprotective therapy could significatively influence disease course are few (Cummings, 2017; Wubben et al., 2019). To assess the efficacy of a therapy, the gold standard endpoint has been considered for a long time the evaluation of visual acuity, but with the improvement of knowledge, it became clear that other endpoints are required (Schmetterer et al., 2023). Meaningful endpoints should include functional, biochemical and structural parameters or any combination thereof. As a matter of fact, several potential endpoints specific for the examined pathology have been proposed, but their validation is complex and requires solid scientific evidence. Thus, the identification of combined endpoints is an urgent need to assess the ratio between risk and benefit of novel interventions (McCoy, 2018; Schmetterer et al., 2023).

2. Glaucoma as neurodegenerative disease

Glaucoma is a chronic neurodegenerative disease characterized by progressive excavation of the optic nerve head (ONH), RGCs axonal injury and corresponding vision loss (Kang and Tanna, 2021). It is one of the major causes of poor vision worldwide in the elderly and it is a social health emergency whose impact is destined to increase over time. It is estimated that it will approximately affect 112 million people worldwide by 2040 (Quigley and Broman, 2006; Tham et al., 2014). The molecular mechanisms underlying the onset and progression of the disease are not fully understood. Thus, treatment is symptomatic and does not drastically change the disease course.

2.1. Pill on glaucoma pathogenesis

Several risk factors for glaucoma have been identified including older age, genetic background, African American ethnicity, diet, lifestyle (*i.e.* aerobic exercise and mindfulness), microvascular diseases like diabetes mellitus and elevated intraocular pressure (IOP) (Coleman and Miglior, 2008; Kumar and Ou, 2023; Tribble et al., 2021a). IOP is considered the most common modifiable risk factor for glaucoma progression. However, in some cases, called normal tension glaucoma (NTG), the ONH damage develops without elevation of the IOP and in other ones the elevated IOP never determines the optic neuropathy, supporting the existence of different pathogenetic mechanisms not exclusively IOP-related (Dahlmann-Noor et al., 2010; Weinreb et al., 2014). According to the mechanical theory, prolonged elevated IOP causes mechanical stress and deformation of the lamina cribrosa (LC), a thin structure composed of collagen fibres, that allows the passage of the RGC axons which converge to form the ONH (Dias et al., 2022; Hakim et al., 2023). The LC is the weakest point in the wall of the pressurized eye, therefore its compression compromises the retrograde transport of neurotrophic factors (see Section 3.1) to the RGC soma, progressively leading to RGCs apoptosis (Chidlow et al., 2007; Weinreb et al., 2014). RGCs death is recognized as the earliest histological manifestation, and the degeneration of up to 36% of RGCs determines the appearance of glaucomatous visual field defects (Kerrigan-Baumrind et al., 2000; Parisi et al., 2018). On the other hand, the vascular hypothesis states that the glaucomatous optic neuropathy may be a consequence of insufficient blood supply related to increased IOP or to factors, other than IOP, that

Box 1
links between Alzheimer's and glauco

The retina is considered an extension of the brain, hence diseases affecting one organ could mirror the other. Given that both glaucoma and AD are typical of elder age, and are the result of neuron degeneration, several studies are focusing on the identification of possible links between glaucoma and AD. One of the goals of these studies is to use the retina as an accessible insight into brain pathology, that could help the diagnosis of AD at an early stage, establishing a therapeutic plan that could slow down disease progression (Gupta et al., 2021).

In support of this idea, epidemiological studies showed that in the population of AD patients, the prevalence of glaucoma is higher than in the control group. These studies took into account also IOP showing that among AD patients, elevated IOP is always associated with glaucoma. Moreover, glaucoma was also found in AD patients without high IOP (Bayer et al., 2002), suggesting that AD patients are more sensitive to retinal degeneration. The structural alterations of the eyes found in AD patients included a reduction in retinal nerve fiber layer (RNFL) thickness, broad axonal degeneration of the optic nerve, and degeneration of retina neurons (Gao et al., 2015; Hinton et al., 1986; Paquet et al., 2007). In addition to these structural modifications, molecular markers typical of AD, such as the accumulation of β amyloid (Aβ) (Hart et al., 2016; Koronyo et al., 2017) and Tau protein (den Haan et al., 2018) were also found in several retinal layers. The possibility to use Aβ and Tau in the retina as biomarkers for AD is under discussion (reviewed in (Liao et al., 2021), but many studies agreed on the fact that Aβ and pTau accumulation is toxic not only for the brain but also for the retina.

Another approach for a better understanding of the link between glaucoma and AD is based on the possibility that glaucoma patients have a major risk to develop AD. A study carried out in South Korea, found that in the group of open-angle glaucoma, there was a higher incidence of AD than control group (Moon et al., 2018). Similar results were also obtained in an 8-year follow-up study (Lin et al., 2014). Given the results of a population-based, retrospective case-control study, Lai et al. also proposed glaucoma as a non-cognitive manifestation of AD disease (Lai et al., 2017). However, further analyses are necessary to understand why others did not show a high incidence of AD in glaucoma patients (Ou et al., 2012).

Overall, AD and glaucoma are both multifactorial diseases, for which genetic seems to be an important risk factor. Among the genetic factors associated with AD or glaucoma, the gene encoding for the Apolipoprotein E (APOE) raised interest in the field, because it seems to be a common risk factor for both diseases, even though is not causative. APOE works as a transport protein for lipids and cholesterol, and it is mainly produced in the liver, but it is also expressed in the brain and retina. The gene *ApoE* has three variants called E2, E3 and E4 differing only in two amino acids, that change the binding preferences for lipoprotein particles, and they are present in the plasma at different levels. APOE4 isoform is the stronger genetic risk for AD, while APOE2 seems to have a protective role. Unexpectedly, epidemiological studies suggested that APOE2 and APOE4 are risk and protective factors for retinal degenerative diseases, respectively. How and why the different APOE isoforms contribute to neurodegeneration is still under investigation, but it seems to be correlated with lipid metabolism, inflammation and clearance of Aβ and Tau aggregated (reviewed in (Abyadeh et al., 2023; Martens et al., 2022)).

In conclusion, AD and glaucoma share several features both at molecular and clinical levels, but further studies are needed to better understand the link and develop new strategies for the prevention and treatment of these neurodegenerative diseases.

induce a reduction of the ocular blood flow (OBF) (Burgoyne et al., 2005; Flammer et al., 2002). Studies dealing with blood flow reported a reduced OBF in all part of the eye, including iris, retina, choroid, ONH, and retroocular vessels in glaucoma patients compared with normal subjects (Flammer et al., 2002; Flammer and Mozaffarieh, 2007). Unstable OBF may be caused by IOP fluctuation, unstable blood pressure and dips that are linked to ONH damage and consequent visual field defects (Grieshaber and Flammer, 2005). Indeed, primary vascular dysregulation, also known as vasospastic syndrome, is considered an important risk factor for glaucoma, especially NTG. Patients with vasospastic syndrome tend on average to have lower blood pressure and perfusion pressure and, also, instability of the OBF autoregulation (Dahlmann-Noor et al., 2010; Emre et al., 2004; Flammer et al., 2002). The major consequence of blood flow compromission is an ischemia and reperfusion damage which may play a role in RGCs death (Chidlow et al., 2007; Grieshaber and Flammer, 2005). Currently, there is no curative treatment for glaucoma, but disease progression can be halted by lowering IOP. Large treatment controlled studies have repeatedly demonstrated that lowering IOP protects against glaucomatous optic nerve damage and visual field loss regardless of subtype or disease stage (Gordon and Kass, 2018; Leske et al., 2004; Miglior et al., 2005; "The Advanced Glaucoma Intervention Study (AGIS)," 2000; "The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group," 1998). However, even when IOP is lowered, some patients continue to progress and suffer of visual impairment and deterioration in quality of life. Studies have reported a rate of blindness from glaucoma despite treatment from 20% to 27% for one eye and 9% for both eyes (Almasieh and Levin, 2017; Hattenhauer et al., 1998; Oliver et al., 2002). Many medications have been approved by regulatory agencies (i.e., FDA and EMA) as IOP lowering therapies acting by reducing aqueous humour (AH) production, improving outflow or a combination of both, even though their administration does not significantly modify the disease course (See Box 2).

2.2. Molecular aspects of glaucoma as a neurodegeneration of the brain

In recent years rather than being considered as a "simple" eye disease, glaucoma is regarded as a progressive neuropathy with damage occurring in other parts of the central nervous system (CNS) (Jane W. Chan et al., 2021; Neacş;u and Ferechide, 2022). Primate models and post-mortem analysis in humans have demonstrated the atrophy of neurons of magnocellular and parvocellular lateral geniculate nucleus (LGN) as well as degeneration of multiple vision area of the brain, including visual cortex (Dai et al., 2011; Yücel et al., 2001). These changes are related to the severity of disease. The neurodegenerative process is not limited to the visual pathways but also extends into areas related to memory, attention, orientation, coordination, and face recognition (Chang and Goldberg, 2012a; Nuzzi et al., 2018). Controversial issues concern whether brain changes are secondary to the optic neuropathy or whether glaucoma begins as primary CNS pathology and, therefore, it can be viewed as a neurological disorder (Lawlor et al., 2018). In fact, even though evidences in primates show that irreversible LGN abnormalities precede RGCs death, the studies are not robust and further investigations are required (Lawlor et al., 2018). It is obvious that if this will be confirmed, a significant reconsideration of the most appropriate therapeutic strategy is required. An archetypal pathological hallmark of neurodegenerative disorders is the destruction of specific

Box 2
IOP reducing, indirect neuroprotective agents in the cure of glaucoma

Over the last decades, researcher's attention has focused on RGCs degeneration, and several molecules have been under investigation in pre-clinical studies for their neuroprotective role (see Section 3) (Chang and Goldberg, 2012b). Interestingly, some of these agents have a positive effect on glaucoma by means of both neuroprotection and IOP reduction and are didactically defined as "indirect neuroprotective agents" (Fogagnolo and Rossetti, 2011; Marcic et al., 2003). The highest reduction of IOP is obtained with prostaglandin (PG) $F_{2\alpha}$ analogues, followed by non-selective β-blockers, Rho kinase inhibitors, alpha-adrenergic agonists (see Section 3.2), selective β-blockers and at last topical carbonic anhydrase inhibitor ("European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition," 2021).

Prostaglandin analogues

Prostaglandin analogues increase the uveoscleral outflow by remodeling extracellular matrix within the ciliary muscle and surrounding sclera, thereby increasing their permeability (Almasieh and Levin, 2017). They may be considered the first-choice antiglaucoma medication having the highest IOP-lowering effect between 20% and 35% from the initial value (Schmidl et al., 2015). Preclinical studies reported that PG analogues have the additional effect to protect neurons. Yamagishi et al. showed a direct neuroprotective effect of PG analogues on glutamate- and hypoxia-induced RGC death using rat purified primary RGC culture with latanoprost acid, travoprost acid, bimatoprost acid, bimatoprost, tafluprost acid, unoprostone, and PGF2a. The mechanisms by which PG analogues exert this effect is not well clarified but seems unrelated to FP receptor stimulation (Yamagishi et al., 2011). Bimatoprost probably prevents from RGCs loss via the Akt pathway, latanoprost rescues retinal neurons and/or glial cells from apoptosis through the pro-survival p44/p42 mitogen-activated protein kinase pathway, and unoprostone via activation of big potassium channels which prevents Ca (2+) dysregulation such as that induced by glutamate excitotoxicity (Cuppoletti et al., 2007; Nakanishi et al., 2006; Takano et al., 2013).

Moreover, the topical administration of travoprost, as for dorzolamide (see below), possesses neuroprotective potential by attenuating HMGB1 upregulation and calmodulin downregulation in an inherited glaucoma model in rats (Schallenberg et al., 2012).

Experimental studies on rabbit have also found that PG analogues, such as tafluprost, travoprost and latanoprost, significantly increased ONH and retinal blood flow and inhibited endothelin-1 induced vascular contraction without IOP reduction (Akaishi et al., 2010; Kurashima et al., 2010).

Beta-adrenoreceptor antagonist (β-blockers)

Beta-blockers reduce aqueous humour production in the ciliary body by decreasing intracellular cAMP concentration thus, inducing a IOP reduction between 20% and 25% from the initial values (Schmidl et al., 2015). In addition to this well-known IOP-lowering effect, preclinical studies have shown that beta-adrenoreceptor antagonists may play a role against RGCs death even if the clinical relevance of this effect remains unclear (Gross et al., 2000; Osborne et al., 1997, 2005; Wood et al., 2003; Zhang et al., 2003). Topical application of betaxolol, a selective β_1 adrenoreceptor antagonist, is able to protect retinal neurons *in vitro* and ganglion cells *in vivo* from the adverse effects of experimentally induced ischemia/reperfusion injury and/or excitotoxicity (Wood et al., 2003; Zhang et al., 2003). It exerts this action by direct interaction with L-type voltage-dependent calcium channels and voltage-sensitive sodium ones, thus reducing calcium and sodium ion influxes into RGCs (Osborne et al., 2005; Wood et al., 2003). Metipranolol and timolol, two non-selective β-adrenoreceptor antagonists, have also the ability to confer neuroprotection to retinal neurons because they possess a certain degree of calcium and sodium channel blocking activity which is, however, less pronounced than that of betaxolol (Wood et al., 2003).

Carbonic anhydrase inhibitors (CAIs)

Carbonic anhydrase inhibitors reduce the aqueous humour production providing an IOP-lowering effect between 15% and 20% from the initial value (Schmidl et al., 2015).

Studies have reported that CAIs increase ONH, choroidal and retinal blood flow and may normalize retinal blood flow regulation in patients with glaucoma acting as neuroprotective agents (Fuchsjäger-Mayrl et al., 2005; Rolle et al., 2008; Schmidl et al., 2015).

Moreover, dorzolamide seems to have an IOP-independent effect on the retina metabolism at proteomic level in an inherited rat glaucoma model (Schallenberg et al., 2012).

The topical administration of dorzolamide attenuates HMGB1 upregulation and calmodulin downregulation in the glaucomatous retina, factors that may play a role in the degenerative events initiated by IOP elevation (Schallenberg et al., 2012).

However, it is unclear if topical CAIs exert a clinically relevant neuroprotective effect.

Rho kinase inhibitors

Rho kinase inhibitors alter actin cytoskeleton and cell motility of trabecular meshwork, canal of Schlemm and ciliary muscle enhancing the aqueous humour outflow (Cholkar et al., 2015). They also increase the OBF to the ONH through vascular smooth muscle relaxation leading to vasodilation (Rao and Epstein, 2007).

Besides the IOP-lowering effect, evidences have pointed out the role of Rho kinase signaling in neuroprotection and axonal development, maintenance and regeneration (Tanna and Johnson, 2018; Van de Velde et al., 2015). This protective role is mediated through the regulation of elements of the axonal cytoskeleton, including actin, microtubules, and intermediate filaments as well as by controlling the inflammation mediated by activation of nuclear factor-kB (Tanna and Johnson, 2018).

A study by Shaw et al. showed that, the topical application of a Rock/Net kinase inhibitor (AR-13324) effectively determines a reduction of RGC loss and induces axonal regeneration of the ONH following optic nerve injury (Shaw et al., 2017).

Parasympathomimetics: pilocarpine

Parasympathomimetics determine a 20–25% reduction of the IOP from baseline by increasing aqueous humour outflow through the trabecular meshwork (Almasieh and Levin, 2017).

Pilocarpine seems to have a non IOP-related neuroprotective effect. *In vitro* and *in vivo* studies on retinal neurons of rats reported that topical administration of pilocarpine, through the activation of muscarinic M1 receptors, appears to attenuate the glutamate-induced neurotoxicity and to reduce the inner retinal damage caused by ischemia/reperfusion injury in a dose-dependent manner (Tan et al., 2014; Zhou et al., 2008).

neuronal populations; for example, in PD, the selective loss of nigrostriatal dopaminergic neurons translates into a progressive movement alteration, and, in AD, the loss of hippocampal and cortical neurons leads to memory and cognitive impairments. Similarly, as already mentioned, visual dysfunction results from RGCs apoptosis with axonal degeneration in glaucoma. RGCs damage is the result of both retrograde and anterograde (or Wallerian) axonal degeneration as well as transsynaptic (transneuronal) degeneration of the injured tract. Retrograde degeneration leads to loss of the cell bodies in the retina, whereas the Wallerian one results in degeneration of all connected visual pathways (Calkins, 2012; Dias et al., 2022). Although the molecular mechanism that triggers selective RGCs damage remain largely unknown, several IOP-unrelated processes have been identified spanning from neuroinflammation, mitochondrial dysfunction, alteration of carbohydrate and lipid metabolism, oxidative stress (see Section 3.5), calcium dyshomeostasis (see Section 3.4), glutamate excitotoxicity (see section 3.2), alteration of autophagy and protein misfolding (Jane W Chan et al., 2021; Duarte, 2021; Duyckaerts et al., 2009; Gupta and Yücel, 2007; Kumar and Ou, 2023; Musa et al., 2023; Quaranta et al., 2021; Sbardella et al., 2021; Tribble et al., 2021a). It is likely that neuroinflammation is one of the major contributors to the development of neurodegenerative diseases. Anyway, even though mounting evidence suggests a role of neuroinflammation also in glaucoma, its contributions is not fully characterized yet (Jane W. Chan et al., 2021; Pinazo-Durán et al., 2020; Quaranta et al., 2021). High level of inflammatory mediators as well as reactive oxygen species (ROS) have been found in AH and blood of diseased patients. The onset of inflammation in glaucoma is hypothesized to be triggered by an altered crosstalk between RGCs and glial cells. Immunohistological and immunohistochemical studies indicate overactivation of glia and astrocytes at the optic nerve head. This phenomenon is associated with the secretion of matrix metalloproteases (MMPs) and a variety of cytokines that are thought to drive the remodeling and excavation of optic nerve head. Moreover, the release of proinflammatory cytokines (IL-1, IL-6, TNFα) and chemokines (CCL2, CX3CL1) was reported at the first central relay level (lateral geniculate bodies and superior quadrigeminal colliculi) (Howell et al., 2013; Huang et al., 2010; Quaranta et al., 2021; Sawada et al., 2010, p. 2). In eucaryotic cells a significant source of ROS is mitochondria, mainly in the context of age-related deterioration of mitochondrial electron chain transfer. Retina is one of the most metabolically active tissues of our body and mitochondria integrity is required to respond to RGCs metabolic demands. In animal models of glaucoma, a number of evidence supports that early metabolic alterations might underscore RGCs degeneration (Harder et al., 2020; Harun-Or-Rashid et al., 2018; Tribble et al., 2021a). Moreover, mitochondrial function may progressively decline as a consequence of aging and exposure to several endogenous and environmental stressors that disrupt mitochondrial homeostasis and lead to the release of multiple mitochondrial damage associated molecular patterns (DAMPs). Neuronal DAMPs can act as inducers of chronic inflammation in glaucoma. In fact, they can trigger inflammatory responses when recognized by complement molecules and microglial pattern-recognition receptors, thus inducing the transcription of proinflammatory cytokines and chemokines. Then, inflammation can further induce mitochondrial dysfunction, thereby amplifying a vicious cycle of inflammation. However, the precise mechanism of how mitochondrial DAMPs lead to glaucomatous neurodegeneration is yet to be fully dissected (Duarte, 2021). Protein misfolding and accumulation is the key pathogenetic event of neurodegeneration, overlapping also with glaucoma. In human glaucomatous retinas, β-Amyloid (βA) deposits and intraneuronal accumulations of hyperphosphorylated tau protein as well as a decrease of Aβ level in vitreous were reported. Moreover, abnormal accumulation of these proteins was demonstrated in animal models of ocular hypertension. Interestingly, no evidence of Tau transcriptional alteration has been envisaged. As a matter of fact, it has been hypothesized that Tau accumulation in retina could be due to impairment in its degradation by UPS or autophagy and/or spreading. Mis-sorting of anterograde axonal transport leads to Tau accumulation into dendrites with concomitant damage (Chiasseu et al., 2016; Gupta et al., 2008; Yan et al., 2017; Yoneda et al., 2005).

3. Neuroprotection in glaucoma: a glance to the future

For most optic neuropathies, treatments are ineffective and do not modify the disease course. As previously mentioned, this therapeutic lacuna has prompted many groups (no profit laboratories, organizations and companies) to investigate the effect of neuroprotective therapies (Monteiro et al., 2017). Noteworthy, metabolic decline prevention has been recently proposed as a viable therapeutic strategy in combination with existing IOP-lowering approaches in the management of glaucoma progression. As recently and extensively reviewed elsewhere, interventions include: exercise, mindfulness, alternative energy sources such as lactate/pyruvate, increment of metabolic cofactors such as NAD and dietary supplements, modifying lipid metabolism through ketogenesis, administration of semaglutide (Jabbehdari et al., 2021; Kumar and Ou, 2023; Tribble et al., 2021a). Neuroprotection encompasses two main strategies, referred to as direct or indirect strategies. Direct neuroprotection refers to approaches targeting RGCs, astrocytes, glia, or both, and, thus, it is not specific for the pathology. The scientific hypothesis driving this strategy is that, whether RGCs (or related ones) structure and function are preserved, vision can be also maintained. On the other hand, indirect neuroprotection is strongly related to the molecular basis of the disease and include therapies that themselves may not act directly on neuronal or glia cells (Levin, 2018; Levin et al., 2022). In the case of glaucoma, some lowering IOP drugs are considered indirect neuroprotective agents since the effect in slowing down the intraocular pressure reduces the rate of RGCs loss (see BOX 2). As matter of fact, current treatments of glaucoma effectively control concomitant ocular hypertension, but do not or poorly affect the progression of neurodegeneration (Calkins, 2012; Fry et al., 2018). Actually, there is no effective treatment that limits the reduction of vision acting on RGCs depletion (Oliveira-Valença et al., 2020). This highlights the need of investigating novel therapeutic approaches. In the next paragraphs, the molecular and pharmacological properties of the most promising direct neuroprotective agents will be examined.

3.1. Neurotrophic factors

Neurotrophic factors (NTFs) exert a neuroprotective effect mediating

axon regeneration and improving neuronal function into the brain (Chang and Goldberg, 2012a). In healthy conditions, RGCs, that express the Trk receptor family, receive neurotrophic support from Muller glia and/or directly from the brain through retrograde axonal transport. According to the "neurotrophin deprivation hypothesis", a defect in neurotrophin support is one of the triggers that induces retinal degeneration and death in glaucoma and, therefore, the administration of NTFs is an appealing therapeutic strategy (Chitranshi et al., 2018; Dekeyster et al., 2015; Johnson et al., 2009). Several NTFs have been associated to glaucoma progression, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factors (GDNF), and neurturin (Ji et al., 2004; Koeberle and Ball, 2002; Lambiase et al., 2009; Oddone et al., 2017). Studies on rat model of glaucoma have confirmed that NTFs could be effective in preventing RGCs death (Kuo and Liu, 2022). NGF and its receptors are expressed in the anterior and posterior segments of the eye and alteration in its expression and signaling are correlated with the onset and/or severity of different ocular pathologies. The neuroprotective mechanism of NGF is associated with oxidative stress inhibition, achieved via the phosphatidtlinositol-3-kinase (PI3K)/AKT survival pathway and with a key role in controlling intracellular calcium levels. In fact, it mediates the presynaptic uptake of calcium that stimulates the presynaptic release of the neurotransmitter, fundamental for synaptic plasticity (Hill et al., 2021). Based on preclinical studies and since NGF is considered a putative target also for other neurodegenerative diseases (*e.g.,* AD), NGF has attracted interest in the cure of glaucoma (Wang et al., 2014). However, an 8-weeks phase 1 b clinical trial (NCT02855450) evaluating the safety and efficacy profiles of recombinant human NGF eyedrops in glaucoma patients revealed the absence of major adverse events and a good tolerability, but not significant short-term neuroenhancement in terms of structural and functional measures (Beykin et al., 2022). The authors proposed that the inconsistency of these results with those obtained in animal model (Lambiase et al., 2009) might be attributed to the treatment duration, since RGCs regeneration could require a time longer than 3 months to achieve a substantial neuroprotective effect. BDNF is produced by RGCs and astrocytes, and its effects are mediated mainly by binding to high-affinity receptor (TrkB) constitutively expressed in the retina and lamina cribrosa. BDNF deprivation triggers apoptosis of RGCs via JNK-mediated signaling, resulting in activation of proapoptotic BCL-2 family of proteins which culminates with mitochondrial dysfunction (Lambuk et al., 2022). Numerous evidences supports BDNF role in glaucoma pathogenesis (Feng et al., 2016; Mysona et al., 2017). In fact, in experimental models of glaucoma retrograde transport defects have been implicated in the progressive development of optic neuropathy (Chitranshi et al., 2018, 2019; Guymer et al., 2019a; Osborne et al., 2018). Moreover, *in vivo* studies have suggested that deficits of BDNF expression mark the RGC damage. Reduced serum and AH level were reported in patients with NTG and POAG (Cha and Kim, 2021; Oddone et al., 2017). Additionally, BDNF serum level were found increased 3 months after trabeculectomy in POAG patients, suggesting that this neurotrophin could be a potential biomarker for disease evaluation (Uzel et al., 2018). Exogenous, topical, or intravitreal applications by injection of recombinant protein or by gene therapy of BDNF were found to be potent in activating the survival of RGCs in ocular hypertension animal models (Domenici et al., 2014; Ji et al., 2004; Mysona et al., 2017; Wójcik-Gryciuk et al., 2020). As mentioned elsewhere (see Box 1 and Section 2), amyloid-beta -related alterations like those observed in the brains of AD individuals, have been found in glaucomatous retina. Interestingly, intravitreal administration of BDNF prevents amyloid-beta RGC apoptosis by activating the BDNF-TrkB signaling pathway in rats (Lambuk et al., 2022; Lazaldin et al., 2023). Nevertheless, more studies are required to highlight the relationship between glaucoma and BDNF as well as whether BDNF supplementation might be an effective neuroprotective therapy for the disease. Moreover, it would be interesting to better explore its possible relevance as a biomarker of treatment outcomes and prognosis for both glaucoma and AD (Lambuk et al., 2022).

CNTF is expressed in glial cells of peripheral and central nervous systems and promote survival in a broad range of neuronal cells which express the CNTF receptor, sustaining neurite outgrowth. CNTF level is reduced in AH and lacrimal fluid in patients with POAG (Shpak et al., 2017). Notably, exogenous CNTF exerts neuroprotection on photoreceptors and RGCs in animal models of various eye diseases (Müller et al., 2009; Pease et al., 2009; Wen et al., 2012). Indeed, several methods have been proposed to deliver CNTF to the retina, including viral transposons and intravitreal injection. Recently, a polymeric device, namely NT-501, has been developed consisting of encapsulated human cells genetically modified to secrete CNTF that can be surgically implanted (Do Rhee et al., 2022). Clinical trials of NT-501-encapsulated cell therapy are currently exploring its therapeutic efficacy. A phase 1 trial enrolling POAG patients indicated, similarly to previous reports in other eye pathologies, that there were no serious adverse effects related to the surgical procedure, intraocular implant, or CNTF secretion (NCT01408472) (Goldberg et al., 2023). Based on these data, a randomized, sham controlled, masked, phase 2 clinical trial in glaucoma, examining dual NT-501 implantation, is underway (NCT02862938 and NCT04577300) (Goldberg et al., 2023).

3.2. NMDA receptor antagonists

Glutamate excitotoxicity is thought to play an important role in a broad variety of neurological disorders including AD, since excessive stimulation of N-methyl-D-aspartate (NMDA), one of the three ionotropic glutamate receptor subtypes, leads to neurons damage and death (Almasieh et al., 2012; Crabbé et al., 2019; Vorwerk et al., 2004). NMDA receptors are widely expressed in the retina, even though under physiological conditions, homeostatic mechanisms prevent their overexpression (Osborne et al., 2018). Excessive glutamatergic insult is linked to the loss of RGCs followed by several retinal injuries, including ischemia, that underscore the progression of diabetic retinopathy, and glaucoma (Almasieh et al., 2012; Crabbé et al., 2019; Vorwerk et al., 2004). Analysis of vitreous composition reveals an increase of glutamate level in different models of glaucoma, even though some controversial results still exist (Brooks et al., 1997; Carter-Dawson et al., 2002; Dreyer et al., 1996). Anyway, the drivers of glutamatergic injury remain partially unknown, but multiple pathways have been implicated, such as alterations of the Na^+/K^+ homeostasis and high level of calcium ions influx into cells (Christensen et al., 2019; Fahrenthold et al., 2018). Increment of intracellular Ca^{2+} activates several enzymes, including phospholipases, endonucleases, and proteases, which can, in turn, damage cell structures such as the cytoskeleton, cell membrane, and DNA (Dutta and Trapp, 2011). Moreover, it can determine apoptosis through activation of a cAMP response element binding (CREB) protein shut-off (Christensen et al., 2019; Dutta and Trapp, 2011; Hardingham et al., 2002; Doozandeh and Yazdani, 2016; Lotery, 2005). MK801 (dizocilpine maleate), a potent non-competitive NMDA antagonist, has been tested as neuroprotective agent in experimental glaucoma. However, its high affinity for the NMDA receptor and long half-life may result in disruption of the glutamate physiological function, leading to neurotoxicity. For this reason MK801 has never been evaluated in clinical trials (Chaudhary et al., 1998; Guo et al., 2006). Memantine is an open-channel blocking NMDA antagonist with moderate affinity that binds only to channels that have been activated by glutamate. Importantly, it effectively blocks glutamatergic pathway at concentrations that do not affect normal neurotransmission and it is approved by FDA and EMA for the treatment of moderate-severe AD and PD (Chen and Lipton, 1997). Several preclinical studies have shown that memantine reduces excitotoxicity in animal models of glaucoma (Hare et al., 2001; WoldeMussie et al., 2002). Although promising results in preclinical models were obtained, a phase 3 randomized, double-masked, placebo-controlled clinical trial in which memantine was administrated daily

over 48 months, reported no significant effect in preserving visual function in glaucomatous patients (NCT00141882 and NCT00168350) (Weinreb et al., 2018). Despite the failure, these large 4-year studies have provided considerable insights regarding the design of future studies, such as the identification of the study population and progressive risk factors, as well as the specific schedule of treatment. In this regard, Weinreb and colleagues suggest that earlier memantine treatment in a population defined by more restrictive risk factors (*e.g.*, age) may produce different effects, revaluating memantine' s role in the treatment of glaucoma (Weinreb et al., 2018). In order to overcome the side effect of systemic memantine administration, topical formulations of memantine-loaded PLGA-PEG nanoparticles were investigated and revealed efficacy and tolerability as well as reduction of systemic side effects in glaucoma models (Sánchez-López et al., 2018). The results that indicate limited efficacy of memantine in glaucoma patients have raised the need of new NMDA receptor antagonists. In this context, bis (7)-tacrine demonstrated a more potent neuroprotective effect in RGCs cells as well as a concurrent inhibition of acetylcholinesterase and nitric oxide synthase. This agent should be deeper investigated to evaluate its potentiality as effective neuroprotective agent in glaucoma (Doozandeh and Yazdani, 2016; Fang et al., 2010).

3.3. The α_2-adrenergic agonist, brimonidine

Alpha$_2$-adrenergic agonists are responsible of the induction of smooth muscle contraction and vasoconstriction. Topical administration of α_2-adrenergic agonists reduces the AH production through vasoconstriction in the ciliary body and increases uveoscleral outflow by contraction of the ciliary muscle leading to a IOP reduction of 20–25% from the initial value (Almasieh and Levin, 2017; Schmidl et al., 2015). Brimonidine tartrate is a third generation α-2 adrenergic agonist used in POAG patients, being in general well tolerated. It shows more than 1000-fold selectivity for α-2 over α-1 receptors, giving it a greater advantage over the first- and second-generation agonists by reducing the risk of systemic side effects (such as systemic hypotension, bradycardia and sedation) as well as reducing the α-1 mediated ocular side effects (such as conjunctival blanching, mydriasis and eyelid retraction) (Cantor, 2000; Schnichels et al., 2021). Brimonidine penetrates the cornea, and, in line with others α_2-adrenergic agonists, it acts by reducing AH production, and stimulating its outflow through the uveoscleral path. Several studies have also suggested that brimonidine provides a non-IOP related neuroprotective effect on visual field deterioration Galanopoulos and Goldberg (2009). In fact, animal models of optic nerve crush or the ischemic retinal injury have demonstrated that α2-agonist has neuroprotective properties in optic nerve degeneration (Dai et al., 2013; Fujita et al., 2013; Lee et al., 2012; Sun et al., 2017). Additionally, systemic administration of brimonidine provided RGCs neuroprotection with little effect on IOP also in chronic ocular hypertension models (Dong et al., 2008; Hernández et al., 2008; WoldeMussie et al., 2001). Even though α_2-adrenergic receptors have been identified in the RGCs, the molecular basis of this novel proposed function is partially unknown (Oh et al., 2019). Brimonidine seems to promote ganglion cell survival, protecting them from degeneration caused by mechanical or ischemic injuries trough neurotrophic factor BDNF induction (see Section 3.1) (Gao et al., 2002). Activation of the α2-adrenoceptor by brimonidine also upregulates glutamate transporters (*i.e.*, EAAT1), and downregulates NMDA receptors (*i.e.*, GluN1) in ocular hypertension animal models, inhibiting glutamate accumulation, and, thus, reducing the glutamate-toxic effects on RGCs (see Section 3.2) (Conti et al., 2021; Jung et al., 2015). Interestingly, it has been also proposed that brimonidine could induce a decrease of Aβ level acting on amyloid precursor protein homeostasis. This reduction interferes with Aβ mediated RGC apoptosis (Nizari et al., 2016). Moreover, its administration inhibits nitric oxide synthase and the endothelin pathway, reducing oxidative stress and glial activity (Guymer et al., 2019b; Khatib and Martin, 2017). Despite the encouraging preclinical results, to date, clinical trials have failed to translate neuron protective action in humans and large trials with adequate statistical power and methodological uniformity are urgently required (Scuteri et al., 2020; Sena and Lindsley, 2017).

3.4. Calcium channel blockers

As mentioned in Section 3.2, the neurotoxic effect, which follows NMDA receptor activation, is mediated by calcium influx into neural cells (Araie and Mayama, 2011; Stout et al., 1998). Thus, it is not surprising that the administration of calcium channel blockers (CCBs) has attracted interest as neuroprotective strategy in visual neurodegeneration, including glaucoma (Crish and Calkins, 2011). CCBs seems to protect RGCs preventing the rate of apoptosis determined by calcium influx and inducing vasodilatation (Crish and Calkins, 2011; Kuo and Liu, 2022). As a matter of fact, it has been reported that various CCBS, including the L-/N-type channel blocker amlodipine and nimodipine, the T-type channel blocker amiloride, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor blockers, and purinergic receptor blockers affect RGCs survival, reducing axonal degeneration, and stimulating axonal regeneration (Otori et al., 2003; Ribas et al., 2017; Savigni et al., 2013; Selt et al., 2010; Yamada et al., 2006). Small-scale studies demonstrate CCBs benefits in glaucoma patients but effects on visual function preservation are still controversial (Cheung et al., 2017; Duan and Liu, 2022; Hu et al., 2021; Koseki et al., 2008, 1999, p. 199). In fact, drawbacks of CCBs use in glaucoma, which can explain these conflicting results, include *(i)* CCBs-mediated vasodilation could direct blood flow away from damaged tissues, and *(ii)* the reduction of systemic pressure could reduce blood flow to the retina, exacerbating the optic nerve damage in glaucoma patients. Thus, additional studies must be performed to improve CCBs selectivity toward RGCs neuroprotection, preventing systemic effects (Araie and Mayama, 2011; Kuo and Liu, 2022; Yilmaz et al., 2020).

3.5. Antioxidant agents

Among the mechanisms triggering neuronal degeneration, oxidative stress seems to play an important role. Oxidative stress occurs when there is the accumulation of reactive oxygen species (ROS) that cannot be eliminated by the antioxidant machinery of the cells. ROS are the natural products of aerobic metabolism, but they can also be produced in response to environmental stressors. Overaccumulation of ROS causes the peroxidation of lipids, affecting the fluidity of the cell membrane, and of other macromolecules, such as proteins and DNA, bringing the cell to death by apoptosis. Several pieces of evidence suggest that oxidative stress participates in glaucoma pathogenesis directly affect RGCs, but also the trabecular meshwork (TM), whose functionality is critical for retinal survival. Hence, antioxidant molecules are under investigation to limit or prevent neuronal degeneration, slowing down glaucoma progression.

The great source of antioxidants is the plant kingdom, in fact, chemical compounds extracted from different plant organs have been tested as treatment for several neurodegenerative diseases with promising results. The extracts of *Ginkgo biloba* leaves, one of the most ancient living trees on the planet, have been used as medicine since ancient times for multiple purposes. Even though many types of extracts are present on the market, the EGb761 is the standardized extract used in most pre-clinical and clinical trials, containing 24% of flavonoids and 6% of terpene lactones. EGb761 acts as an antioxidant because of its scavenger activity on ROS (Chen et al., 1999), but it also increases the activity of the antioxidant cell machinery acting on the superoxide dismutase (SOD) enzyme (Bridi et al., 2001) and glutathione (GSH) levels (Rimbach et al., 2001). Moreover, EGb761 defends mitochondrial metabolism from damage caused by oxidative stress (Eckert, 2005). Many preclinical studies showed that EGb761 protects retinal ganglion cells from degeneration caused by different stresses, such as hypoxia

(Cho et al., 2019), optic nerve degeneration (Ma et al., 2010) and elevated IOP (Hirooka et al., 2004), inhibiting cell apoptosis (Di Meo et al., 2020).

Another compound with antioxidant activity coming from plants is resveratrol. Resveratrol is a polyphenol present in many fruits, such as blueberries, cranberries, and grapes. This polyphenol compound acts as a ROS scavenger (Gülçin, 2010), but it may act as an antioxidant because it modulates the expression of several genes that are part of the antioxidant machinery of the cell (Xia et al., 2017). Cao et al. showed that resveratrol preserves mouse RGCs from the degeneration caused by elevated IOP, decreasing the levels of ROS and increasing SIRT1 levels (Cao et al., 2020), a well-known anti-aging protein with a protective role against oxidative stress (Singh et al., 2018). Similar results were also obtained in the glaucomatous rat model with high IOP (Pirhan et al., 2016) and in retinal cell lines subjected to high pressure (Zhang et al., 2018), confirming the neuroprotective effect of resveratrol. Another cellular target of resveratrol is the TM, where a reduced antioxidant capacity has been associated with the progression of primary angle glaucoma. TM cells undergoing oxidative stress caused by H_2O_2 show a reduced metabolic activity, which is restored by pretreatment with resveratrol (Ammar et al., 2012; Luna et al., 2009), suggesting that administration of resveratrol could prevent the damages caused by oxidative stress.

The plant *Crocus sativus*, commonly known as saffron, has great commercial value not only because it is a tasty spice used for food preparation, but also for its medical properties. The stigma of saffron contains multiple bioactive metabolites and, among these, safranal and crocin seem to be the components with antioxidant properties since they show radical scavenging activity (Assimopoulou et al., 2005). Oral administration of crocetin, as well as safranal, prevents retinal degeneration in animal models of glaucoma (Fernández-Albarral et al., 2019; Fernández-Sánchez et al., 2012; Ohno et al., 2012), pointing out that the saffron extracts, used as a diet supplement, can act as neuroprotectors. Besides the antioxidant properties (Farahmand et al., 2013; Wang et al., 2019; Yamauchi et al., 2011), saffron extracts protect cells from apoptosis, also controlling the inflammatory pathway, decreasing the morphological signs of microglial activation (Fernández-Albarral et al., 2019) and the levels of cytokines (Li et al., 2023), typical of an inflammation state.

Two non-plant-based compounds that show antioxidant properties are citicoline and Coenzyme Q10 (CoQ10). Citicoline (cytidine-5′-diphosphocholine) is a natural intermediate in the synthesis of phospholipids, key components of the cell membranes. When citicoline is ingested, it is hydrolyzed into cytidine 5′-diphosphate and choline, which are translocated in the brain through the blood–brain barrier, where they are used to re-synthesize citicoline in neurons. Citicoline was proposed as neuroprotector because it increases the release of the neurotransmitters dopamine and norepinephrine, improving the functioning of the nervous system. However, the molecular mechanism underlying citicoline effect is still under investigation, and recent studies pointed out the possible role of citicoline in ameliorating cell response to oxidative stress. In TM cells stressed by H_2O_2, citicoline treatment diminishes ROS levels and H_2O_2-induced apoptosis, in agreement with the reduced levels of pro-apoptotic proteins (Vernazza et al., 2022). Similar results were also obtained in the neuron-like cell lines PC12 (Aminzadeh and Salarinejad, 2019) and SHSY5Y (Barrachina et al., 2002, 2003) where citicoline restored SOD and GSH levels affected by oxidative stress, improving cell viability. Moreover, citicoline is a modulator of the activity of proteasome, which is the cell machinery committed to protein degradation after ubiquitylation (Sbardella et al., 2020b). Proteasome degrades proteins during their natural turnover, but it also plays an important role in recognizing and eliminating oxidized proteins that are produced because of ROS accumulation. Hence, the stimulation of proteasome activity by citicoline could help the restoration of cell homeostasis through the clearance of oxidized proteins. In addition to the molecular data, experiments in animal models and cell lines confirmed the neuroprotective effects of citicoline towards damaged RGCs (reviewed in (Parisi et al., 2018). All this evidence together led to the design of many clinical studies that aim at evaluating citicoline activity in glaucoma patients. dministration of citicoline as intramuscular or oral solution improved RGCs function with an enhancement of the neural conduction along the visual pathways and visual field (Parisi, 2005; Parisi et al., 1999, 2008). Lately, citicoline was proposed as eye drops solution to facilitate the administration to patients and ensure local absorption. In fact, upon administration of eye drops, citicoline was found in the vitreous of treated patients (Carnevale et al., 2019), suggesting that it can penetrates the eye tissues. This result, together with the improvement of the visual defects and RGCs survival observed in the glaucomatous patients treated with the ophthalmological solution (Parisi et al., 2015, 2019), endorse citicoline as treatment of glaucoma with a neuroprotective activity.

Coenzyme Q10 (CoQ10), which is present in the mitochondria, where it participates in the electron transport chain for ATP production, is an antioxidant with scavenging activity, which improves cell response to oxidative stress reducing cell loss (Lee et al., 2014; Noh et al., 2013). Interestingly, CoQ10 levels decrease in the retina of elderly people (Qu et al., 2009), suggesting that its deficiency could be correlated with age-related retinal diseases and hence its administration could prevent neurodegeneration. Eyedrops of CoQ10 with vitamin E positively affect the cortical visual of patients with open-angle glaucoma (Parisi et al., 2014). The same eyedrops were also used in a study on pseudo-exfoliative glaucoma: patients receiving the treatment showed lower levels of SOD in the aqueous humour compared to untreated patients, confirming the antioxidant role of CoQ10 (Ozates et al., 2019). Lastly, among molecules that exert antioxidative properties, we mentioned erythropoietin (EPO), a circulating hematopoietic hormone responsible for erythropoiesis, whose receptors are expressed in retina, including photoreceptor cells, retinal pigment epithelium, and retinal ganglion cell layer (Lin et al., 2022). It seems to cover additional multiple roles, such as cognition improvement, neurogenesis, anti-fibrotic, anti-apoptotic, anti-inflammatory and, mainly, antioxidative effects. It has been demonstrated that EPO increases levels of heme oxygenase-1 and glutathione peroxidase, reducing oxidative stress. Accordingly, several studies have suggested its therapeutic potentiality in different human neurodegenerative diseases (Rey et al., 2019). Alteration of EPO production is associated with glaucoma; in facts, it is reported that its level increases in the aqueous humour, but not in plasma of affected subjects (Tribble et al., 2021a). Moreover, EPO crosses the blood–brain barrier and blood–retinal barrier to exert its neuroprotective action on CNS and eye and, thus, the therapeutic effect has been studied both locally and systemically in glaucoma, as recently reviewed elsewhere in great detail (Grimm et al., 2002; Lai et al., 2023).

Notably, all the molecules presented exert their neuroprotective role without altering IOP, which is one of the main risk factors of glaucoma, hence antioxidative compounds could be used to improve the results obtained with the drugs that decrease IOP.

3.6. Nicotinamide

Niacin is a precursor of the coenzyme nicotinamide adenine dinucleotide (NAD^+) which is essential for healthy mitochondrial metabolism and several cellular processes. Since the local absence of myelinated axons in the intraocular portion of the optic nerve leads to high energy requirements, RGCs are particularly vulnerable to any energy deficit and mitochondrial dysfunction, as also mentioned in the previous section (Morgan, 2012). Not by chance this important risk factor of glaucoma has been identified in both animals (Williams et al., 2017) and glaucoma patients (Tribble et al., 2019).

Different studies on DBA/2 J (D2) mouse model of glaucoma identified an age-dependent depletion of retinal levels of NAD^+ that renders RGCs susceptible to IOP-related stress. As a result, investigations began about the effect of NAD^+ repletion in the same animal model. Both

dietary supplementation of nicotinamide (NAM), the amide of niacin, and viral gene-therapy overexpressing Nmnat1 (a terminal enzyme for NAD production) have been successfully used to correct NAD^+ decline and to reduce progressive optic nerve degeneration (Williams et al., 2017, 2018).

Glaucoma patients have also been found to have systematically low serum levels of NAM (Kouassi Nzoughet et al., 2019). The above findings, in addition to the events observed in the D2 mouse model, have opened promising therapeutic perspectives based on nicotinamide supplementation. Pure NAM preparation reveals an excellent safety profile also at high doses, being the side effects mainly due to impure preparation containing also niacin (Knip et al., 2000). The safety profile of vitamin B3 reports a low incidence of side effects and toxicity, including high doses (Knip et al., 2000). Currently there are two different trials to watch out for. The Glaucoma Nicotinamide Trial (TGNT) is a prospective, randomized, placebo-controlled, double-masked trial (NCT05275738) that has started in May 2022, with a projected end date of December 2026, in which POAG patients will be randomized to two groups: receiving NAM (1.5 g/day for the first 6 weeks and then 3.0 g/day) or placebo (Umeå University, 2022). The Nicotinamide in Glaucoma Trial (NAMinG) is a phase 3 randomized, placebo-controlled, multi-centre trial (NCT05405868) that will start in September 2023 and with an estimated end date of November 2026. In this trial, participants will receive NAM for up to 27 months (1.5 g/day for the first 6 weeks, then the dose increases to 3.0 g/day for 21 weeks) or placebo, in addition to an initial treatment of standard of care IOP-lowering therapy (University College, London, 2023).

Noteworthy, since, as previously mentioned, preclinical studies have suggested that enhancing mitochondrial function and administration of alternative energy source as pyruvate should be beneficial for RGCs survival (Harder et al., 2020), a combination of nicotinamide and pyruvate has been tested in a phase 2, randomized, double-blind, placebo-controlled clinical trial (NCT03797469). This combined therapy yielded a short-term improvement in visual function in patients with treated, manifest glaucoma, as measured with standard automated perimetry, supporting a role for these agents in neuroprotection and confirming the need for long-term studies (De Moraes et al., 2022). In summary, NAM provides important neuroprotective effects by increasing oxidative phosphorylation, buffering and preventing metabolic stress, preserving mitochondrial motility and simultaneously damping the potential firing rate of neurodegenerative action (Tribble et al., 2021b). However, the results of large-scale clinical trials are still awaited, before NAM can be considered an accepted therapeutic modality for glaucoma.

3.7. Statins

Statins, as 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, represent the first-line therapy for the treatment of hyperlipidemia and cardiovascular diseases (Chou et al., 2016). Their major mechanism of action is related to inhibition of cholesterol synthesis. Interestingly, in a meta-analysis of observational studies an association between glaucoma and high total cholesterol and low HDL levels was reported, supporting the hypothesis that alteration of lipid levels is an additional risk factor for glaucoma development (Posch-Pertl et al., 2022). In a retrospective longitudinal cohort study, a group treated with statins showed a lower incidence of POAG compared to the no statin group (Stein et al., 2012). Moreover, administration of statins has been associated with visual field improvement in patients with normal tension glaucoma and open-angle glaucoma (Kim et al., 2021; Whigham et al., 2018). However, controversies still exists, since other studies showed no or poor statistically significant association between statin use and rates of structural and functional changes in glaucoma subjects as well as glaucoma progression (Kang et al., 2022; Yuan et al., 2022). Recently, statins have also received attention as candidates for glaucoma treatment given their neuroprotective effects. In preclinical models of chromic ocular hypertensions, it has been reported that statins improve RGCs survival, reducing apoptosis and suppressing glia activation (Kim et al., 2021, p. 202; Schmeer et al., 2008). The precise molecular mechanism of the neuroprotective effect of statins needs to be further studied.

4. Concluding remarks

Currently, there are several neuroprotective agents under investigations for the treatment of glaucoma and some of them have produced positive results in preclinical models. Anyway, different factors contribute to the successful translation of novel glaucoma treatments into clinical practice. The main barriers to this may include the heterogeneity in phenotypical manifestations of the disease as well as the limited knowledge on the molecular mechanisms underscoring its onset. This statement reflects also the intrinsic difficulty in developing reliable animal models of the diseases due to variability in outcome measurement, differences in ocular bioavailability, and optimal timing of intervention (Lambuk et al., 2022). Therefore, a better understanding of the molecular basis of the pathology and the differences in nerve damage across the different forms of glaucoma gains overwhelming relevance (Kong et al., 2023). Another key aspect concerns the design of clinical trials. In general, trials are carried out with patients already receiving IOP-lowering treatments, whilst the effect of these strategies should be investigated in newly diagnosed glaucoma. Additionally, the cohort of enrolled patients is often too heterogeneous. Sometime, the duration of the observation period is also short. However, little information on potential interactions between the different classes of medications is available, and neuroprotective mechanisms could require a long period of observation to be assessed in terms of therapeutic efficacy. Furthermore, the efficacy maybe relevant in just one sub-group of patients but ineffective in the other one. Thus, the identification of early biochemical and structural biomarkers that highlight the accurate efficacy of these novel treatments is mandatory (Hill et al., 2021). The failure of trials concerning some drugs and the success of other ones could be strongly related to a series of factors that should be taken into considerations before unequivocally evaluating the drug efficacy (Garway-Heath et al., 2015). As a consequence, alternative clinical trial designs may be useful to better understand the effective impact of novel medications and to maximize the chances of providing new sight-saving therapies for patients. Furthermore, development of formulations circumventing anatomical barriers and allowing a suitable and compliant route of administration remains challenging.

Glossary

Neuroprotection includes a broad range of strategies that prevent the loss of neurons and/or their connection when the disease is ongoing or when it does not yet occur.

Neurorestoration encloses strategies aimed at the replacement of different components of existing neurons or the activation of their residual functionality in order to repair the damage.

Neuroregeneration refers at therapies aimed at forming new neuronal circuitry, mainly by generation of new synapses and/or novel neurons from extrinsically provided stem cells (*i.e.*, embryonic or pluripotent) or from intrinsic ones (such as reprogramming Muller glia cells to become retinal ganglion cells in retina).

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