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REVIEW ARTICLE

Novel Therapeutics in Glaucoma Management

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Abstract: ***Background*:** Glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell death and alterations of visual field. Elevated intraocular pressure (IOP) is considered the main risk factor of glaucoma, even though other factors cannot be ruled out, such as epigenetic mechanisms.

***Objective*:** An overview of the ultimate promising experimental drugs to manage glaucoma has been provided.

***Results*:** In particular, we have focused on purinergic ligands, K_{ATP} channel activators, gases (nitric oxide, carbon monoxide and hydrogen sulfide), non-glucocorticoid steroidal compounds, neurotrophic factors, PI3K/Akt activators, citicoline, histone deacetylase inhibitors, cannabinoids, dopamine and serotonin receptors ligands, small interference RNA, and Rho kinase inhibitors.

***Conclusions*:** The review has been also endowed of a brief chapter on last reports about potential neuroprotective benefits of anti-glaucoma drugs already present in the market.

Keywords: Glaucoma, anti-glaucoma drugs, intraocular pressure, retinal ganglion cells, purinergic ligands, Rho kinase inhibitors, dopamine ligands, nitric oxide, histone deacetylase inhibitors.

1. INTRODUCTION

Glaucoma is an optic neuropathy characterized by retinal ganglion cell (RGC) death and irreversible peripheral and central visual field loss. The WHO epidemiologic analysis identified glaucoma as the second worldwide leading cause of irreversible blindness, accounting for 12% of blindness cases [http://www.who.int/blindness/causes/en/]. The causes of glaucoma have not been univocally identified, yet. Intraocular pressure (IOP), above 21 mmHg, is the most recognized risk factor of glaucoma; the higher is the IOP, the greater the likelihood of glaucoma. Primary open angle glaucoma (POAG) is a commonly bilateral disease of adult onset and it is characterized by high IOP, optic nerve damage and visual field loss. POAG is the most prevalent type of glaucoma. Primary angle-closure glaucoma (PACG) is less common, the terms "angle closure" refers to occlusion of the trabecular meshwork by the peripheral iris obstructing aqueous outflow. Elevated IOP can cause a "mechanical damage" of the optic nerve head (ONH) and then RGCs death. Beside POAG and PACG, there are patients with normal-tension glaucoma (NTG) that is usually regarded as a variant of POAG. NTG is characterized by IOP equal to or less than 21 mmHg, optic nerve damage, an open anterior chamber angle and visual field loss. Any etiological factors distinct from those in POAG have not been conclusively assessed, even though various mechanisms have been suggested, including anomalies in vascular function and in the structure of optic nerve [1, 2]. It is noteworthy that some NTG patients have been found to have marked nocturnal IOP spikes [1, 3]. Furthermore, recent findings supported the mechanical damage of glaucoma, because OHN compression was found to be related to decreased cerebral spinal fluid pressure, along with increased stiffness of sclera and lamina cribosa connective tissue, particularly in NTG patients [4, 5].

Because POAG patients could benefit IOP lowering medical interventions, glaucoma is considered by the World Health Organization (WHO), an avoidable cause of blindness, and the disease is listed within the Priority Eye Diseases of WHO.

2. NEUROPROTECTION

Besides existence of IOP lowering medical interventions, including pharmacological treatments and ocular surgery procedures (*e.g.* trabeculectomy), the awareness about glaucoma should not decrease, because symptoms occur when most of the RGCs die.

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Nowadays, the unmet medical need in glaucoma is related mainly to: i. ambiguous etiology of glaucoma; ii. late diagnosis; iii. disease progression (RGC death) despite IOP control.

Thus, research of new drugs should not only be focused on IOP lowering agents, but also on neuroprotective molecules (Fig. **1**).

While basic research is currently looking for neuroprotective agents, clinical development of neuroprotective drugs for glaucoma has decreased due to several reasons such as: i. uncertain mechanism of pathogenesis disease; ii. uncertain therapeutic targets; iii. unpredictable glaucoma animal models; and iv. limited reliable clinical functional end-points [6]. Progression of visual field loss is, generally, used as a functional endpoint in clinical trials, aiming at evaluation of neuroprotective effects of drugs in glaucoma patients. However, because progression of glaucoma is slow and visual field progression has shown high intra- and inter-patient variability, clinical trials for assessment of efficacy of neuroprotective drugs would need longer time (at least 4-5 years), that means high costs and business risks. With these perspectives, pharmaceutical industries would not easily invest in neuroprotection programs [6]. Another critical point of the choice of visual field loss progression as functional clinical endpoint is that visual field loss occurs when about 50% of RGCs are dead [6]. Thus, basic research is currently focused on validation of new methods for early diagnosis of glaucoma, aimed at the evaluation of RCGs death or dysfunction, that can be evaluated by means of in-vivo retinal imaging and electrophysiological studies [7-9]. Recently, pattern electroretinogram (PERG) amplitude was found to be an innovative functional endpoint for evaluation of RGCs functionality in patients with suspected glaucoma [10]; because PERG amplitude, an index of RGCs dysfunction, was found to be decreased before RGCs death and related structural modification at ONH [11].

A typical example of lack of valuable functional endopoints in clinical trial is represented by the memantine study. After phase III, memantine, a NMDA receptor antagonist, was not further developed as glaucoma treatment, simply because no significant difference was found between the placebo and the drug [12]. The failure of memantine clinical trial had a bad impact on further development of this drug, and in general on investments on neuroprotective agents by pharmaceutical companies [13]. However, this failure in 2008 has not stopped the research and development of new neuroprotection strategies for glaucoma; thus, we have reported in this review the latest updates on basic preclinical and clinical research results on neuroprotective agents for glaucoma.

The recent review by Levin and co-author (2017) confirmed that the main anatomical targets of putative neuroprotective drugs are RGCs, and sites that promote RGCs survival such as Müller cells, astrocytes and retinal microvascular cells [14]. Moreover, other anatomical targets, according to the mechanical hypothesis of glaucoma, are the sclera [15-18] and sites of production and drainage of aqueous humor (AH) [1]: ciliary bodies (site of production of AH-inflow) and trabecular meshwork (site of drainage of AH-outflow).

Several biochemical pathways and pharmacological targets have been explored in order to obtain neuroprotection [19]. Glutamate receptors are recognized as the main pharmacological targets of neuroprotective drugs, because uncontrolled activation of glutamate receptors leads to neurodegeration (exicitoxicity cascade); thus memantine, a NMDA receptor antagonist, was first developed for Alzheimer's disease and then for glaucoma [19]. There is a general consen-

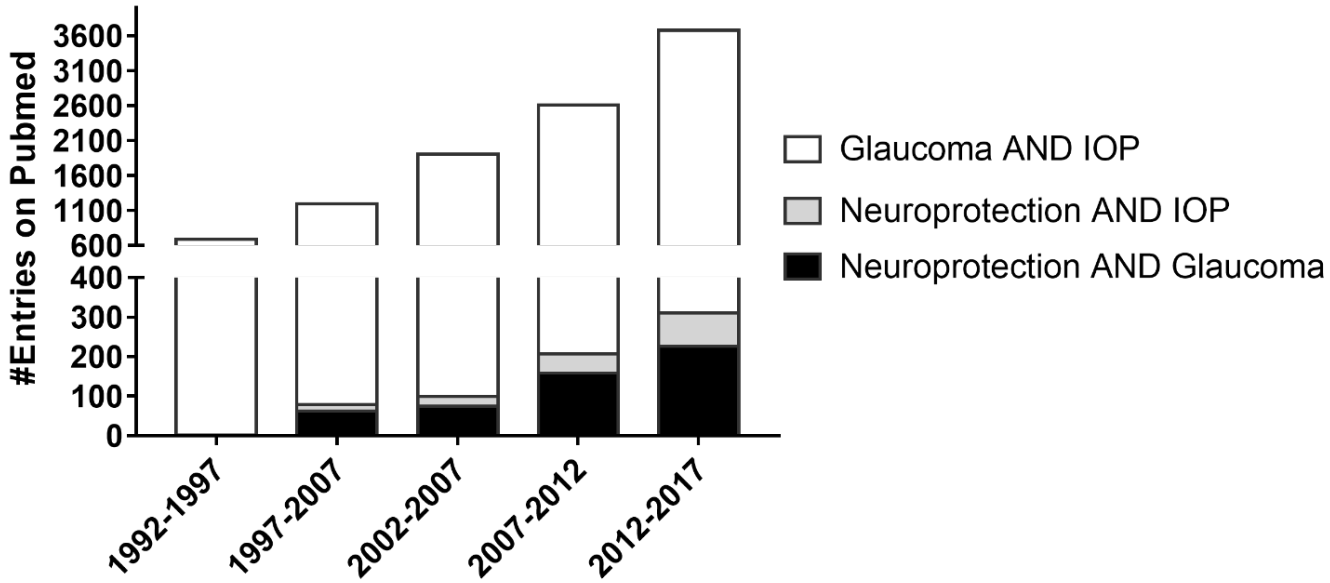

Fig. (1). PubMed entries on neuroprotection strategy and glaucoma treatment. Entries have been retrieved from PubMed using the following formula in the advanced search PubMed engine: "search terms"; YYYY:YYYY [edat]; (*e.g.* "glaucoma AND IOP"; 2007:2012 [edat]).

sus that development of memantine was mainly doomed due to the trial design, rather than the lack of drug efficacy; therefore, the strategy of excitotoxicity cascade inhibition should not be totally abandoned by neuroscientists and ophthalmologists.

3. PURINERGIC LIGANDS

There is an increasing interest about purinergic receptors as pharmacological targets to manage glaucoma [20]. The adenosine A_1 receptor (A_1R) agonist INO-8875 (*i.e.* trabodenoson developed by Inotek pharma) [1] was able to decrease IOP by increasing AH outflow [21], and was recently evaluated in a phase III multi-center, randomized, double-masked, active-(0.5% timolol) and placebo-controlled study [NCT02565173]. However, this study had only one clinical endpoint, *i.e.* the IOP assessment. Visual function measurement in a future clinical study with trabodenoson, can be of value, because it was found that A_1R activation promoted RGCs survival in an *in vitro* model of inflammatory damage [22] and promoted protective effects in a variety of *in vitro* and *in vivo* models of CNS neurodegeneration [23-25]. The adenosine A_2R agonist, OPA-6566, reached the phase I/II in a clinical trial [NCT01410188] [1]; however, we were not able to retrieve any information about further development of this drug. Within the adenosine receptors, the A_3R might exert modulation of the exicitotoxicity cascade, as suggested by recent reports on A_3R agonists [26, 27]. Recently, it was found that A_3R activation prevented RGCs death in both *in vitro* and *in vivo* models of optic neuropathy [28]. 2-Cl-IB-MECA, an A_3R agonist, decreased the number of apoptotic cells treated with kainic acid and NMDA, furthermore, this compound promoted RGCs survival in retinal ischemia-reperfusion injury and in partial optic nerve transection models [28]. However, the role of A_3R in glaucoma is still controversial, for instance PBF-677, an A_3R antagonist, has been developed for glaucoma treatment (NCT02639975). Furthermore, it was found that either adenosine A_3 receptor genetic knockdown [29] or its pharmacological inhibition led to decrease of IOP [30]. On the contrary, CF101, an A_3R agonist, originally developed as an oral anti-inflammatory agent for dry eye, was able to decrease IOP in glaucomatous patients [31]. Actually, CF101 is being developed for glaucoma (NCT01033422). The controversies about involvement of A_3R in IOP regulation could be related to the "inversion effect", which was found to be a typical characteristic of adenosine receptors, as it was theorized by Jacobson and co-authors (1996) [32]. Indeed, the "inversion effect" can explain why the pharmacological effect of an adenosine ligand, administered in acute, can be totally inverted when it is administered chronically. Since glaucoma therapy is chronic, the "inversion effect" should be taken into account in a trial that involves A_3R or other adenosine receptor ligands.

The neuroprotective action of A_3R agonists may include the reduction of intracellular [Ca^{2+}] release, due to the activation of purinergic P2X7 receptor [33-35]. Therefore, P2X7 antagonists can be potentially useful as neuroprotective agents in glaucoma [19]. P2X7 antagonists increased RGCs survival after NMDA challenge (intravitreal injection) [36]. On the contrary, P2X7 activation promoted the mechanosensitive release of IL-3, leading to RGCs survival through activation of the IL-3Rβ receptor. Therefore, P2X7 activation can have a role in retinal protection in case of non-ischemic IOP elevation [37, 38], however, several experimental models of glaucoma highlighted that P2X7 activation could have detrimental effects on RGCs survival [39-43].

4. K_{ATP} CHANNEL ACTIVATORS

K_{ATP} channels are inward-rectifying potassium channels that modulate membrane excitability on the basis of the metabolic state of the cell, because K_{ATP} channels are inhibited by micromolar concentrations of intracellular ATP. K_{ATP} channels subunits Kir6.1, Kir6.2, and SUR2B are expressed in the trabecular meshwork [44]. Activators of K_{ATP} channels (diazoxide and nicorandil) decreased IOP in rats and mice [44, 45] by increasing AH outflow, through trabecular meshwork (TM) or uveo-scleral pathway. Additionally, KR-31378 (K_{ATP} channel opener) was found to protect RGCs in a rat model of chronic retinal ischemia [46]. KR-31378 is a synonymous of DNB-001 developed by Danube Pharmaceuticals Inc. This compound was tested in a phase I/II trial assessing safety and efficacy of DNB-001 by oral route in naïve patients with ocular hypertension [NCT00683501]. However, no further development steps of DNB-001 have been reported, so far. K_{ATP} openers are generally hydrophobic compounds and this characteristic is a common barrier for development of K_{ATP} openers delivered in aqueous eye drops formulations, which are commonly preferred for chronic treatment of glaucoma [47]. However, pharmaceutical technology research is now focusing on ophthalmic formulation of hydrophobic drugs encapsulated into solid lipid nanoparticles or nanostructured lipid carriers, these nanoparticle formulations have shown high loading capacity, high ocular drug availability, high stability and good ocular safety [48, 49].

5. GASEOUS MESSENGERS

Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulphide (H_2S) are gaseous molecules that have long been considered as highly toxic gases and environment pollutants. Recently, it has been highlighted that a cross-talk with these three gases exist in the eye [50, 51]. Particularly, NO, CO and H_2S regulated IOP and ocular vascular tone.

Preclinical studies reported an increased retinal immunostaining of nitric oxide synthase (NOS), in a rat model of ocular hypertension [52], and, non-selective inhibition of NOS isoforms by systemic administration of L-NAME protected RGCs in a retinal ischemia-reperfusion injury model [53]. In particular, a study on healthy human volunteers revealed that NOS could have a role in basal autoregulation of optic nerve head blood flow (ONHBF), but not when intraocular pressure is experimentally increased [54]. Thus, a study on ONHBF and the effects of NO in POAG patients, would help in understanding the role of NO and NOS in ocular hypertension and glaucoma. Nitric oxide can exert both neuroprotective and neurotoxic effects, generally depending on NO concentration. NO donor compounds were found to be neuroprotective in *in-vitro* and *in-vivo* models of glaucoma [55]; *e.g.* nipradilol (β-blocker with a NO releasing moiety) [56, 57]. However, a comparative clinical study on NTG patients did not highlight differences between the

Table 1. List of compounds under development to treat glaucoma.

Pharmacological Action	Name of Molecule(s)	IOP reduction Mechanism	Neuroprotection Mechanism	Clinical Trial	Phase of Clinical Trial	Clinical Trial Outcomes
A1R agonist	trabodenoson	↑ outflow	Inhibition of neuroinflammation	NCT02565173	III	IOP
A2R agonist	OPA-6566	↑ outflow	N.D.	NCT01410188	I/II	IOP
A3R agonist	2-Cl-IB-MECA	↓ Inflow ↑ outflow	Inhibition of excitotoxicity	N.A.	N.A.	N.A.
A3R agonist	CF101 or IB-MECA, piclidenoson,	↓ Inflow ↑ outflow	Inhibition of excitotoxicity	NCT01033422	II	IOP
A3R antagonist	PBF-677	↓ Inflow	N.D.	NCT02639975	I	safety, PK parameters
P2X7 antagonist	A438079	N.D.	Antiapoptotic ↓ $[Ca^{2+}]_{intra}$	N.A.	N.A.	N.A.
KATP opener	DNB-001	↑ outflow	Inhibition of excitotoxicity	NCT00683501	I/II	IOP
NO releasing molecule/prostaglandin analog	Latanoprostene bunod or PF-03187207, BOL-303259-X, NCX-116, Vesneo™	↑ outflow	Regulation of optic nerve head blood flow downregulation of NMDA functions	NCT00441883	II	Visual function
δ-opiod agonist	SNC-121	N.A.	Inhibition of neuroinflammation	N.A.	N.A.	N.A.
estrogens	17β-estradiol and HE3286	N.A.	Antiapoptotic Induction of BDNF	N.A.	N.A.	N.A.
Neurotrophin	NGF	N.A.	Tissue trophism	NCT02855450	I	Visual function
Neurotrophin	CNTF	N.A.	Tissue trophism	NCT01408472	I	Visual function
Not defined	citicoline	N.A.	Inhibition of excitotoxicity	NCT01338389, NCT03046693		Visual function
HDAC inhibitor	Entinostat	N.A.	Induction of BDNF	N.A.	N.A.	N.A.
Dopaminergic agonist	Dopamine, 8-OH-DPAT, cabergoline	↓ Inflow	Regulation of RGCs physiology	NCT02706977, NCT02837640		Visual function
Serotonergic ligands	AL-37807	↓ Inflow ↑ outflow	Inhibition of excitotoxicity and neuroinflammation	NCT00372931	II	IOP
Cannabinoids	HU-210 WIN55212-2 Cannabis	↑ outflow	Inhibition of excitotoxicity and neuroinflammation	NCT02080676, NCT03078309		Visual function
Small interference RNA	SYL040012	↓ Inflow	N.A.	NCT02250612	II	IOP
Small interference RNA	QPI-1007	N.A.	Antiapoptotic	NCT01064505, NCT01965106	I	Safety, optic nerve structure
Rho kinase and NET inhibitor	netarsudil	↓ Inflow ↑ outflow	Axonal regeneration	NCT02674854, NCT02558374, NCT02558400	III	IOP, visual function

(Table 1) contd….

Pharmacological Action	Name of Molecule(s)	IOP reduction Mechanism	Neuroprotection Mechanism	Clinical Trial	Phase of Clinical Trial	Clinical Trial Outcomes
Rho kinase and NET inhibitor and prostaglandin analog	netarsudil latanoprost	↓ Inflow ↑ outflow	↓ Inflow and inhibition of neuroinflammation	NCT02674854	III	IOP, visual function
β-blocker	timolol	↓ Inflow	Inhibition of excitotoxicity and induction of neurotrophic factors	LoGTS 2011		IOP, visual function
α2 adrenergic agonist	brimonidine	↓ Inflow ↑ outflow	Antiapoptotic	LoGTS 2011		IOP, visual function
prostaglandin analog	latanoprost	↑ outflow	Antiapoptotic and inhibition of neuroinflammation	NTG-X-PERT		IOP, visual function

For references please see the text. NB. Latanoprost, timolol and brimonidine are currently approved as IOP lowering drugs; we included these compounds in the present table because are under evaluation for potential retinal protection activity.

nipradilol and timolol treatment in terms of visual field loss progression [58]. The promising preclinical results about NO-donor compounds, which are capable to decrease IOP by increasing AH outflow, led to development of latanoprostene bunod (LBN) [55, 59]. LNB is a prostaglandin analogue with a NO releasing moiety; LNB is also known as PF-03187207, BOL-303259-X, NCX-116, and Vesneo™. LBN was found to be more effective in decreasing IOP than latanoprost [1, 60], however, its potential neuroprotective effect needs to be further investigated [61]. We have retrieved only a clinical trial (NCT00441883), which evaluated the effect of LBN on visual field (secondary outcome) after 28 days of treatment, however, this time slot was quite short and any potential neuroprotective effect of LNB treatment would not be highlighted. Indeed, further studies about the role of NO and specific NOS isoforms in ocular vascular regulation and neuroprotection of RGCs, are needed.

The effect of NO on modulation of IOP can be also linked to μ3 opioid receptor [62], because it was found that the reduction of IOP after ocular instillation of morphine was reversed by pretreatment with L-NAME [63]. A series of findings might suggest that opioid receptors activation protects the retina from damage associated to different experimental models of glaucoma [64-67]. Three opioid receptor subtypes (δ, κ, μ) were found to be expressed in rat retina [67]. Activation of δ-opioid receptor protects RGCs in an experimental model of elevated IOP inducing a downregulation of inducible NOS (iNOS) [65]. It is noteworthy that δ-opioid receptor activation can counteract neuroinflammation [68], which is detrimental to RGCs function and progression of glaucoma [69, 70].

6. NON-GLUCOCORTICOID STEROIDAL COMPOUNDS

The neuroprotective potential of estrogens was recently extensively reviewed by Engler-Chiurazzi and co-authors (2016) [71]. The estrogen 17β-estradiol (E2) showed protective effects on RGCs in different experimental models of glaucoma [72-74], including the ischemia-reperfusion injury model [75]. Additionally, 17β-estradiol eye drops promoted RCGs survival and preserved visual function in an experimental model of glaucoma without decreasing IOP [76]. Furthermore, a study reported that estrogen levels could affect the risk of glaucoma in women [77]. We have then looked up in literature for molecules with similar properties of estrogens, but bearing poor estrogenic effects and non-glucocorticoid activity. Such lead compound would be 17α-Ethynyl-androst-5ene-3β, 7β, 17β-triol (HE3286) [78], which is a synthetic derivative of dehydroepiandrosterone, that was initially developed as an anti-inflammatory drug to treat diabetes and autoimmune diseases. Dehydroepiandrosterone exerted neuroprotective effects in several preclinical studies [79-83], and its synthetic derivative HE3286 protected optic nerve head and RGCs from damage, in an experimental model of optic neuritis [84]. Furthermore, HE3286 enhanced RGCs survival and expression of brain derived neurotrophic factor (BDNF) in retina and optic nerve head in an experimental model of ocular hypertension; however, HE3286 did not decrease the IOP in glaucomatous rats [85]. Indeed, development of HE3286, or related derivatives, eye drops could be a novelty in the therapeutic glaucoma panorama.

7. NEUROTROPHIC FACTORS

Glaucoma progression could be related to neurotrophins deprivation [86]; interestingly, low serum levels of BDNF and nerve growth factor (NGF) were associated to early-moderate stages of glaucoma [87]. NGF serum levels in glaucomatous patients correlated with visual field modification in comparison to control group, but this correlation was not found between BDNF levels and visual field deviation in glaucomatous patients. The potential therapeutic value of BDNF and NGF to treat glaucoma is noteworthy, and the main point that breaks the development of these factors as eye drops is related to the drug delivery challenges [88]. Local administration such as intravitreal injection of neurotrophic factors cannot be pursued because glaucoma treatment is lifelong. Ocular topical treatment of neurotrophin is challenging due to protein stability and degradation sensitivity, however, besides these problems, human recombinant NGF (hrNGF) ophthalmic formulation (180 μg/ml) is currently

under clinical development in a phase Ib trial for treatment of glaucoma (NCT02855450).

Additionally, the ciliary neurotrophic factor (CNTF), delivered through an intravitreal implant "NT-501", has been recently investigated for treatment of glaucoma in the NCT01408472 clinical trial. CNTF exerted, in several models of RGCs death and optic nerve ischemia, protective effects most likely by means of activation of JAK/STAT, MAPK/ERK, and PI3K/Akt pathways [89]. Furthermore, after optic nerve crush procedure in animals, CNTF treatment led to regeneration of optic nerve axons, and restored the visual function in the animals with damaged optic nerve [90].

8. PI3K/AKT ACTIVATORS

Akt is a downstream component of the phosphoinositide 3-kinase (PI-3K) signaling that exerts prosurvival and anti-apoptotic effects, and glycogen synthase kinase-3β (GSK-3β) is a downstream substrate of Akt. Increased levels of pAKT led to phosphorilation of GSK3β, which was in turn inactivated, leading to RGC survival after ischemic-reperfusion insult [91]. It has been demonstrated that co-administration of forskolin, an adenylate cyclase activator, along with homotaurine and L-carnosine significantly increased pGSK-3β protecting RGCs from ischemic insult [92, 93]. Direct inhibition of GSK3β has been explored as neuroprotection strategy, and tideglusib, a GSK3β inhibitor, was able to protect RCGs from damage induced by intravitreal injection of NMDA [94]. Up-stream activation of the PI3K/Akt pathway can occur at transmembrane receptors such as apelin receptor (APJ) [95], a GPCR, which shares high sequence homology with the angiotensin II receptor. The endogenous ligand of APJ is the 36 aminoacid peptide called apelin, that protected RGCs from damage induced by NMDA when injected intravitreally in rats [96]. Actually, there are ongoing studies on stable apelin analogues [97], as well as small molecules that activate APJ [98, 99].

9. CITICOLINE

Citicoline or cytidine 5'-diphosphocholine might protect RGCs by mimicking neurotrophic factors [100] and by inhibiting excitotoxicity in retinal tissue [101]. Our literature search has highlighted one randomized, prospective and masked study with open angle glaucoma patients, which were treated four months with citicoline eye drops.

Topical treatment (4 months) with citicoline in open angle glaucoma patients induced an enhancement of the retinal function (increase of PERG amplitude) with a consequent improvement of visual cortex activity (shortening and increase of visual evoked potentials (VEP) implicit time and amplitude, respectively) [102]. Previously, Parisi *et al*. (2008) investigated citicoline treatment (oral and intramuscular administration) on retinal function and neural conduction in the visual pathways of glaucoma patients with moderate visual defects [103]. In this study, authors showed that one year-treatment with citicoline improved retinal function (evaluated by pattern electroretinogram recordings) and neural conduction along visual pathways (evaluated by visual evoked potential recordings) in glaucoma patients. Besides the small number of published papers, citicoline has been used as neuroprotective agent for long time and its use for treatment of glaucoma started in the early 2000s, on the basis of ameliorated visual functions reported in patients systemically treated with citicoline [104]. Furthermore, we have retrieved three studies by search "citicoline AND optic neuropathy" on clinicaltrial.gov: NCT01338389; NCT03046693; NCT02984813.

10. HISTONE DEACETYLASE INHIBITORS

The treatment with histone deacetylase (HDAC) inhibitors, in order to increase RGCs survival, was investigated for the first time in 2010 and 2012 by Pelzel H.R. and co-authors [105, 106]. In an experimental (optic nerve crush) and a genetic model of glaucoma (aged DBA/2J$^{R3/R3}$ mice), HDAC3 accumulated in the nucleus and increased the deacetylation of H4 during the early phase of RGCs death. In this study, the inhibition of HDAC resulted in increased RGCs survival. Valproate, a drug currently used to manage seizures, exhibited protective effects on RGCs because is a HDAC inhibitor [107]. This mechanism could be related to increased expression of the BDNF receptor TrkB [107]; however, valproate showed toxic effects on RGCs at high doses [108]. Furthermore, broad-spectrum HDAC inhibitors are characterized by several adverse reactions, that could involve the gastrointestinal tract, immune and cardiovascular systems [109]. Entinostat (MS-275), a selective HDAC1 and HDAC3, showed fewer mild side effects than valproate [110]. Furthermore, entinostat decreased the rate of RGCs loss in retina of animals after optic nerve crush procedure [111]. In this perspective, more efforts should be carried out in order to develop selective HDAC1,3 inhibitors that might have larger therapeutic index in comparison to non-selective HDAC inhibitors [112].

11. DOPAMINERGIC AND SEROTONERGIC LIGANDS

Dopaminergic receptors (DR) belong to a class of aminergic GPCRs; D_2R-like and specifically D_3R agonists were found to be effective in decreasing IOP [1, 113-115]. Pattern electroretinogram (PERG) response of Parkinson's Disease (PD) patients on dopaminergic therapy was better in comparison to PERG response of untreated PD patients, therefore, the hypothesis of dopamine deficiency behind visual dysfunction has been built on the basis of this finding [116]. Furthermore, PERG latencies were found to be delayed in patients on haloperidol therapy [117]. Thus, the dopaminergic system might have a regulatory role in RGCs physiology [118]. Currently, there are no reports on potential neuroprotective effects of dopaminergic agonists in experimental models of glaucoma, however, recent reports showed that dopaminergic agonists exhibited neuroprotection in models of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease [119-121]. Glaucoma might have common pathological features with neurodegenerative diseases of CNS [69, 122], then, dopaminergic agonists capable to decrease IOP might also exert retinal neuroprotection. Our search on clinicaltrials.gov ("dopaminergic agonist AND eye") has highlighted the lack of trials involving dopaminergic agonists for treatment of glaucoma. However, there are clinical trials for investigation of dopaminergic agonist

effects on visual function (primary outcomes: retinal fiber layer thickness, multifocal electroretinography, visual acuity, visual field): NCT01663935; NCT01620164; NCT00812760. Interestingly, we found that carbidopa/levodopa combination is currently being under evaluation for improvement of visual function in patients with diabetic retinopathy [NCT02706977] and retinitis pigmentosa [NCT02837640].

The class of serotonergic receptors is a large family, that includes one ionotropic receptor (5-HT_3) and six metabotropic GPCRs (5-HT_1, 5-HT_2, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 receptors). The expression of serotonergic receptors in ocular tissues was investigated, and serotonin receptors were expressed in ocular tissues localized either in the anterior or posterior chambers of the eye, thus the serotonergic system can exert a series of physiological function in the eye [123]. The 5-HT_1, 5-HT_2, and with less extend 5-HT_7 subfamily, have been previously identified as interesting pharmacological targets for modulation of IOP [1, 124, 125]. Two serotonergic ligands reached the phase II of clinical development; however, the development of these two drugs, AL-37807 (Alcon) and BVT28949 (Swedish Orphan Biovitrum), was discontinued. Besides that, serotonergic ligands have a high potential as IOP lowering drugs and protection agents. In fact, it was demonstrated that $5HT_{1A}$ ligands protect RGCs from death in a model of retinal ischemia and after NMDA insult [126], and neurons in others paradigms of neurodegenerative diseases [127, 128].

12. CANNABINOIDS

Cannabinoids can control not only IOP, but they could be interesting neuroprotective compounds. In 1996, Yoles and coauthors reported that dexanabinol (HU-211) exerted neuroprotective action in a model of optic nerve injury [129]; however, despite its structural similarity to cannabinoids, dexanabinol it was characterized as NMDA antagonist [130] and NFκB inhibitor [131]. HU-210, the enantiomer of HU-211, exhibited neuroprotective activity in a genetic model of retinitis pigmentosa (P23H rats) [132]. Furthermore, chronic treatment with (–)-Δ9-tetrahydrocannabinol (Δ9-THC), administered through intraperitoneal injection, decreased IOP and reduced death of RGCs in experimental model of ocular hypertension [133]. Recently, the ocular pharmacokinetic profile of Δ9-THC soluble prodrug was evaluated *in vivo* [134]. However, 1 h after topical administration to rabbit's eye, this Δ9-THC prodrug was only detected in the anterior segment of the eye, no traces of the drug were determined in the back of the eye [134]. Indeed, Δ9-THC prodrug eye drops would be innovative IOP-lowering agent, but due to the poor bioavailability to the back of the eye could not able to protect RGCs.

Additionally, it was found that the activation of CB1 and TRPV1 receptors by WIN 55212-2 and methanandamide exhibits retinal protection [135].

The role of TRPV1 receptor in glaucoma is still controversial [136-139], however the increasing interest on TRPV1 receptor as pharmacological target to manage glaucoma deserves further investigated.

We have looked up in clinicaltrial.gov database, and retrieved two studies: the first [NCT02080676] has the objective to evaluate IOP and optic nerve structure in marijuana smokers, the aim of the second trial [NCT03078309] is to assess visual function effects of cannabis administration in retinitis pigmentosa patients, in comparison to healthy subjects. These two trials are recent, in particular the NCT02080676 is currently recruiting adult patients with no ocular pathology that are being treated in neurology or pain clinics with medical cannabis. The NCT03078309 is active but is not yet open for patient recruitment. The NCT03078309 will recruit patients with retinitis pigmentosa that will receive the first day a single dose of cannabis (tetrahydrocannabinol:cannabidiol, THC:CBD, 1:40). On the second day the subjects will receive a single dose of cannabis (THC:CBD 1:1) and will be subjected to full ocular exam and visual function assessment. However, after the second day of treatment with cannabis, no further follow-up is planned in NCT03078309 trial, thus long-term effect of cannabis would not be analyzed in retinitis pigmentosa patients. To our knowledge no clinical studies are actually in progress on cannabinoid ligands and glaucoma.

13. SMALL INTERFERENCE-RNA

Small interference-RNAs (siRNA) are small nucleotides able to interfere with mRNA translation into protein. Two siRNAs reached clinical phases of development: SYL040012, which is able to silence the β_2 adrenergic receptor (ADRB2); and QPI-1007 that is able to inhibit caspase-2. SYL040012 works as a beta-blocker and decreases IOP by inhibition of AH production [1]. In a preclinical study, SYL040012 decreased IOP of 20% below the baseline values in albino rabbits for about 7 days [140]. Phase 1 clinical trial on SYL040012 showed that the 600 µg/eye/day dose was more effective in decreasing IOP *vs*. placebo. Particularly, a subgroup of patients treated with 600 µg/eye/day showed a significant IOP decrease, 20% below the baseline values [141]. Low concentrations of SYL040012 were detected in plasma in a non-clinical pharmacokinetic study [140], while no detectable levels of SYL040012 were found in the clinical pharmacokinetic study [141]. In conclusion, SYL040012 can be considered the next-generation beta-blocker, because this siRNA is an effective IOP lowering agent with a better safety profile [1]. Results about a phase 2 trial of SYL040012 (NCT02250612, Bamosiran from Salentys S.A.) are not available yet, however, visual field evaluation was not included either within the primary or secondary endpoints of the study. QPI-1007 caspase-2 inhibitor was developed for treatment of both non-arthritic ischemic optic neuropathy (NAION) and glaucoma. Non-clinical studies showed strong evidences regarding the ability of siRNA caspase-2 inhibitor to increase RGCs survival [142, 143]. A study on QPI-1007 showed that intravitreal injection of the oligonucleotide was well tolerated in rats [144]. Furthermore, after intravenous infusion or bolus administration, QPI-1007 did not exert any microscopic and macroscopic modifications in rats, suggesting low QPI-1007 systemic toxicity [144]. In 2013, a phase I study evaluated the safety of QPI-1007, one year after the single dose intravitreal administration to NAION patients [NCT01064505]. Moreover, QPI-1007 safety and efficacy was evaluated in patients with acute angle-closure glaucoma [NCT01965106]; the study

included visual field evaluation (primary endpoint) up to six months after the first administration [145].

14. RHO KINASE (ROCK) INHIBITORS

Cells of TM have smooth muscle-like properties [146-148]. Rho kinases (ROCK1 and ROCK2) are interesting pharmacological targets to manage glaucoma; these kinases can interact with an high number of proteins belonging to the actomyosin contractile system, named "contractome", which was identified in various non-muscle contractile cells [149], including TM cells. ROCK is a protein kinase that regulates actin and myosin, which are proteins that are responsible for cellular contraction. ROCK activity also promotes the production of extracellular matrix proteins, that help the anchoring of cells to their substrate. In the trabecular meshwork the resistance to AH drainage is regulated by the contraction of TM cells and the production of extracellular matrix components. ROCK inhibitors (ROCKi) block TM cells contraction and reduce the production of extracellular matrix elements, thereby, ROCKi compounds increase aqueous humor outflow, thus decrease IOP.

Over the past few years, many studies have highlighted the essential role of the Rho and Rho-associated coiled-coil protein kinase (ROCK) pathway in the pathogenesis and treatment of glaucoma. Modulation of ROCK activity can be exploited not only for regulation of IOP, but ROCKi can be also used in glaucoma surgery; because ROCK inhibitors bear also anti-scarring activity [150]. A ROCK inhibitor (ROCKi) developed by Aerie Pharmaceuticals (0.02% netarsudil, Rhopressa®) is going to be soon approved by FDA, and it has been previously announced as breakthrough innovative therapy for treatment of glaucoma [1]. The clinical trial NCT02246764 was aimed at comparison of 0.02% netarsudil with 0.5% timolol maleate. This trial included within primary endpoints the ETDRs (Early Treatment Diabetic Retinopathy Study) visual acuity evaluation; however, the results of NCT02246764 are not available yet. Noteworthy, there are several reports that showed the neuroprotective properties of ROCK inhibitors, that were tested in several experimental models of glaucoma [151, 152]. The potential neuroprotective effects of ROCK inhibitors have been recently reviewed by Van de Velde and co-authors (2015) [152]. This review highlighted that ROCK inhibitors will probably be a breakthrough technology for treatment of glaucoma, not only for their strong efficacy in decreasing IOP, but also for their high potential neuroprotective properties, that include the induction of axonal regeneration [152]. Recently, Novack G.D. (2017) reported that Aerie updated the timing of its intended new drug application (NDA) filing of netarsudil (Rhopressa®), as glaucoma treatment [153]. However, a May the 15th 2017 press release announced the FDA acceptance of Rhopressa® NDA [154]. Netarsudil is the first compound belonging to a new "dual action" class of drugs, that are capable to decrease IOP by increasing AH outflow and also by decreasing AH in-flow. In fact, netarsudil can inhibit both ROCK and the norepinephrine transporter (NET) [155]. NET is involved in the presynaptic reuptake of norepinephrine, and inhibits by negative feedback the postsynaptic α_2 adrenergic signaling. Therefore, inhibition of NET leads to prolongation of the α_2 adrenergic signaling, which in turn reduces the production of AH; indeed, a NET inhibitors, such as netarsudil has a mechanism of action similar to the approved IOP lowering drug brimonidine (α_2 agonist). Moreover, Aerie is developing Roclatan®, a combination of netarsudil with latanoprost; thus, Roclatan® efficacy is accounted to reduced AH production, increased outflow through the TM and the uveo-scleral pathway. We retrieved three clinical trial of Rhopressa® and Roclatan ® that included as secondary endpoint the visual field monitoring, with follow-up periods ranging from 3 to 12 months after treatment [NCT02674854, NCT02558374, NCT02558400]. While, the development of netarsudil is advanced in the Aerie pipeline, the compound ripasudil (Glanatec®)(Kowa Company ltd) reached the Japanese market in 2014 [156]. Kowa has licensed D. Western Therapeutics Institute, Inc.; which now has global rights on ripasudil, with exception of Japan. However, the agreement between Kowa and D. Western Therapeutics Institute is mostly undisclosed [156]. Ripasudil decreased significantly IOP in a phase III study (JapicCTI-111564); and the association of ripasudil with either timolol or latanoprost was more effective than timolol and latanoprost monotherapy; these results come out from two Phase III clinical trials JapicCTI-111701 and JapicCTI-111700, respectively [156]. Recently, repasudil, in association with a prostaglandin analog (undisclosed compound), was found to be effective in decreasing IOP in patients with exfoliative glaucoma [157]. We have found only one report on the putative neuroprotective effects of ripasudil, which protected RGCs of C57BL/6J mice subjected to optic nerve crush procedure [158]. In a recent preclinical study, ripasudil has been tested in two experimental animal models of diabetic retinopathy and retinopathy of prematurity, respectively [159]. This study may suggest a new therapeutic indication for Rock inhibitors, *i.e.* ripasudil.

LIM-kinase (LIMK, where LIM is the acronym of the three gene products Lin-11, Isl-1 and Mec-3) is a serine/threonine kinase, that phosphorylates cofilin and regulates actin cytoskeletal reorganization. LIMK, similarly to ROCK, was found to be involved in both remodeling of trabecular meshwork by cytoskeleton re-organization and cell contractility; therefore both LIMK and ROCK inhibition decrease IOP by enlarging the mesh of TM [160, 161]. LX7101 from Lexicon Pharmaceutical, a dual LIMK-ROCK2 inhibitor, reached the phase 1/2a phase [NCT01528111], however, no further development has been reported since 2015. Besides that, a recent study highlighted that LIMK inhibitors may exert a neuroprotective role on photoreceptors, in a model of retinal detachment, therefore, LIMKi development might be redirected to another therapeutic field, rather than glaucoma [162].

15. MARKET APPROVED DRUGS AND NEUROPROTECTIVE EFFECTS

Approved IOP lowering drugs have been further studied in order to claim some neuroprotective effects on RGCs [163]. Within approved drugs for glaucoma, the β-blockers betaxolol, timolol and levobetaxolol exerted retinal neuroprotection in experimental models of glaucoma, such as the ischemic reperfusion injury model. The mechanism of action, through which β-blockers might work as neuroprotec-

tans, could be related to regulation of calcium channels or to induction of neurotrophic factor expression [163]. The effects of timolol on visual function were evaluated in the Low pressure Glaucoma Treatment Study (LoGTS 2011) [13]. The LoGTS 2011 was the main object of the recently published Cochrane Database systematic review, which analyzed clinical trials regarding neuroprotective agents and glaucoma. Particularly, the authors included in the analysis only randomized controlled trials in which topical or oral treatments were applied for neuroprotection in adults with open angle glaucoma (OAG) [13]. The LoGTS 2011 compared 0.2% brimonidine monotherapy with 0.5% timolol monotherapy and one endpoint of this study was the progression of visual field loss. The results of LoGTS 2011 study claimed that brimonidine treated group experienced a slower progression of visual field loss, in comparison to the timolol group. Brimonidine is an adrenergic α_2 receptor agonist that decreases IOP mainly blocking aqueous production [1]. Several preclinical studies proved the neuroprotective effects of brimonidine on RGCs [164-168]. In particular, brimonidine promoted RGCs survival in a model of ocular hypertension by increasing p-BAD (Ser 136) levels and by promoting the Aβ non-amyloidogenic pathway (=increased levels of sAPPα) [169]. Besides the promising results on brimonidine the Cochrane systematic review highlighted that the LoGTS 2011 study could be affected by several bias, related to: i. the exclusion of participants after randomization; ii differences between the two study groups in rate of drop-out during the follow-up period; iii. improper handling of missing data [13]. Additionally, LoGTS 2011 study could be affected of bias in the final published reports, because the primary endpoint was changed between the first report in 2005 and the second paper in 2011 [13]. Furthermore, although evaluated, assessments of visual acuity, optic nerve structure and cup-disc ratio are not reported in the papers about LoGTS 2011 study [13].

The prostaglandin analog latanoprost is an approved IOP-lowering drug able to decrease IOP by facilitating AH outflow, mainly through the uveo-scleral pathway. Several non-clinical studies claimed that latanoprost exerts neuroprotective effects in the retina [170, 171]. A Japanese clinical trial evaluated long term effects (within 5 years) on normal tension glaucoma patients treated with latanoprost monotherapy, and this study reported that after 5 years the 68% of patients experienced no progression of glaucoma [172]. Furthermore, the "Observational Study of the Long-term Effect of Latanoprost in Normal Tension Glaucoma (NTG-X-PERT)" [NCT01209624] evaluated IOP and several parameters related to visual function in patients treated with latanoprost monotherapy; the study results were published only on clinicaltrial.gov. In this review, we have analyzed only one cumulative outcome, *i.e.* the "overall progression of glaucoma damage". The "overall progression of glaucoma damage" was found in 25.8 patients over 469, that were included in the NTG-X-PERT, however, no statistical analysis of NTG-X-PERT results has been already reported. Worthy of note, the NTG-X-PERT was not included in the Cochrane Database systematic review (2017), because it was registered as an observational study [13].

CONCLUSION

The number of non-clinical and clinical studies on new candidates for glaucoma treatment is still growing, and some of these potential innovative drugs will be likely soon approved for clinical use. However, despite the promising results from non-clinical studies, retinal protection remains a "big question mark" both to neuroscientists and clinicians. So far, many molecules showed impressive effects in terms of retinal protection in several paradigms, but no one passed clinical trials. Non-clinical studies on neuroprotective agents have demonstrated significant effects in terms of functional endpoints such as PERG, visual field loss progression and so on. The reasons of that are not so clear, probably because non-clinical studies have relied on evaluation of early outcomes, while clinical trials rely on long follow-up, or perhaps, because most of non-clinical and clinical studies have used narrow time windows during drug treatment, or simply because we need to establish more accurate paradigms that recapitulate the whole retinal damage observed in the clinical condition. In conclusion, translating bench success to bedside has been frustrating for glaucoma scientists but should be, at the same time, a prick to keep going on that.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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