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Review

Combined drug triads for synergic neuroprotection in retinal degeneration

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ABSTRACT

This review focuses on retina degeneration occurring during glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinitis pigmentosa (RP), and on the potential therapeutic use of triads of repositioned medicines, addressed to distinct but complementary targets, to prevent, delay or stop retina cell death. Although myriad pathogenic mechanisms have been implicated in these disorders, common signaling pathways leading to apoptotic cell death to all of them, and to all neurodegenerative diseases are (i) calcium dyshomeostasis/excitotoxicity; (ii) oxidative stress/mitochondrial dysfunction, and (iii) neuroinflammation/P2X7 receptor activation. From a therapeutic point of view, it is relevant to consider the multitarget approach based on the use of combined medicines acting on complementary pathogenic mechanisms that has been highly successful in the treatment of chronic diseases such as cancer, AIDS, pain, hypertension, Parkinson's disease, cardiac failure, depression, or the epilepsies as the basic mechanisms of cell death do not differ between the different CNS degenerative diseases. We suggest the multi-target therapy approach could be more effective compared with single-drug treatments. Used at doses lower than standard, these triads may also be safer and more efficient. After the establishment of a proof-of-concept in animal models of retinal degeneration, potential successful preclinical trials of such combinations may eventually drive to test this concept in clinical trials in patients, first to evaluate the safety and efficacy of the drug combinations in humans and then their therapeutic advantages, if any, seeking the prevention and/or the delay of retina degeneration and blindness.

Abbreviations: A2E, N-retinyl-N-retinylidene ethanolamine; AD, Alzheimer's disease; AGE, advanced glycation end product; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AMD, age related macular degeneration; Ang, angiopoietin; BBB, brain-blood barrier; anti-Aβ, anti-amyloid beta; BzATP, 2,3-O-(4-benzoylbenzoyl)-ATP; CaBP, calcium-binding protein; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CAT, combined antioxidant therapy; Cav, voltage-dependent calcium channels; CICR, Ca^{2+}-induced Ca^{2+} release; CREB, cyclic AMP response element binding protein; CT, clinical trial; CYP, cytochrome P450; DHA, docosahexaenoic acid; DM, diabetes mellitus; DR, diabetic retinopathy; DREAM, downstream regulatory antagonist modulator; EAAT2, excitatory amino acid transporter 2; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERG, electroretinogram; FDA, US Food and Drug Administration; GCL, ganglion cell layer; GluR, glutamate receptor; HCMD, high calcium microdomain; HD, Huntington's disease; INL, inner nuclear layer; IOP, intraocular pressure; IP_3, inositol trisphosphate; IP_3R, inositol trisphosphate receptor; mCU, mitochondrial Ca^{2+} uniporter; mPTP, mitochondrial permeability transition pore; mRGC, melanopsin-containing retinal ganglion cell; MS, multiple sclerosis; NFAT, nuclear factor of activated T-cells; NFL, nerve fiber layer; NMDA, N-metyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; oATP, oxidized ATP; ONL, outer nuclear layer; P2X7R, purinergic P2X7 receptor; PD, Parkinson's disease; PDGF, platelet derived growth factor; PECT, Ca^{2+} efflux transporters; PG, prostaglandin; PK, pharmacokinetic; PKC, protein kinase C; PLC-γ1, phospholipase C-γ1; PPADS, pyridoxal-phosphate-6-azophenyl-2,4-disulfonic acid; PUFA, polyunsaturated fatty acids; RBB, retinal-blood barrier; RP, retinitis pigmentosa; RGC, retinal ganglion cell; ROS, reactive oxygen species; RPE, retinal pigment epithelial cell; RyR, ryanodine receptor; S1P, sphingosine-1-phosphate; TLR, toll-like receptor; TRPC, transient receptor potential canonical; TRPV, transient receptor potential vanilloid; UPR, unfolded protein response; Cav, voltage-activated Ca^{2+} channels; VEGF, vascular endothelial growth factor.

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1. Introduction

The eye retina is a brain tissue. As such, vessels, glia, and neurons are its main constituents. Photoreceptors, bipolar cells, horizontal cells, amacrine cells, and retinal ganglion cells (RGCs) are the neuronal types of the retina. Their disposition in the different retinal layers is schematically displayed in Fig. 1. Located in the outer nuclear layer (ONL) of the vertebrate retina, the photoreceptors rods and cones initiate the phototransduction process of converting light energy into electrical signals. The cell bodies of interneurons (horizontal, bipolar, and amacrine cells), predominantly located at the inner nuclear layer (INL), modify and relay the visual information from photoreceptors to the retinal ganglion cells (RGCs), at the ganglion cell layer (GCL). Their axons initially run in the nerve fiber layer (NFL) to form the optic nerve, conveying the visual signals to the brain to interpret them as visual images [1].

A complex light-sensitive network such as the retina, which is formed by multiple layers of interconnected neurons, exhibits high vulnerability upon its exposure to several types of stress injury. This is exemplified by degenerative diseases primarily originated in the retina as well as those secondary to neurodegenerative diseases affecting different brain tissues. The following are the main eye diseases leading to retina degeneration, which will be discussed in this review: (i) glaucoma, a leading cause of blindness, is associated to augmented intraocular pressure (IOP), degeneration of RGCs, and optic nerve damage; (ii) age-related macular degeneration (AMD), the main cause of irreversible vision loss in the elderly, secondary to dysfunction and loss of retinal pigment epithelial (RPE) cells and photoreceptors, with the stimulation of vascular angiogenesis, an increase in the formation of lipofuscin granules, an accumulation of advanced glycation end products, drusen formation, and breakdown of the blood retinal barrier and changes in pigmentation, altogether with a reduction in melanosomes, increased thickness of Bruch's membrane and mitochondrial DNA deletions; (iii) diabetic retinopathy (DR), a complication occurring in patients with poorly controlled diabetes, blindness is secondary to blood vessels growth on the retinal surface and apoptotic death of RGC, photoreceptors, horizontal or amacrine cells; and (iv) retinitis pigmentosa (RP), a group of inherited diseases leading to blindness, photoreceptor degeneration occurs, being usually the rods affected first, and then cones [2,3].

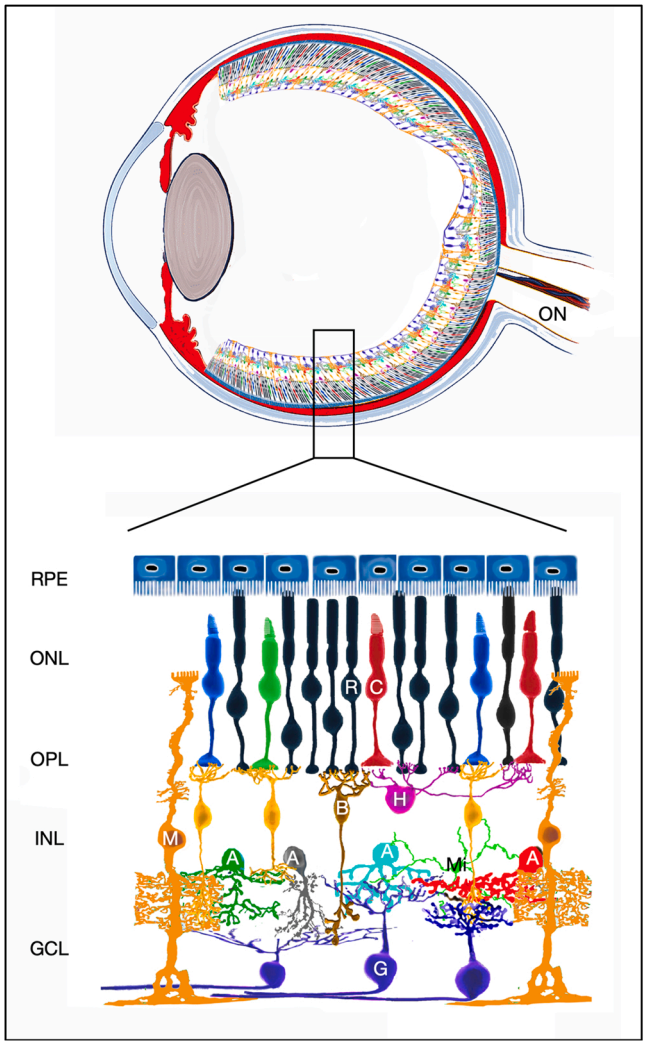

Fig. 1. Retinal cytoarchitecture. An overall view of the eye. Representation of a vertical section of a human ocular globe (top) showing the main retinal layers and cell types (bottom). RPE, retinal pigment epithelial cell; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; GCL, ganglion cell layer; R, rods; C, cones; B, bipolar cells; H, horizontal cells; A, amacrine cells; G, ganglion cells; M, Müller cells; Mi, microglial cells.

Retinal damage secondary to neurodegenerative diseases has also been observed. This is the case of retinopathy in Alzheimer's disease [4] and Parkinson's disease (PD) [5]. In PD, the degeneration of photosensitive melanopsin-containing RGC has recently been associated to disorders of sleep and circadian rhythms [6]. A recent study concludes that, as happens to be the case in striatal dopaminergic neurons, the amacrine dopaminergic neurons also degenerate in the retina of PD patients, thus explaining the visual alterations above mentioned [7].

Myriad receptors, ion channels, intracellular signaling pathways, and mutated proteins have been implicated in neurodegenerative diseases. Several of these pathological hallmarks are also present in the pathogenesis of retinal degeneration.

The basic pathogenic pathways leading to cell death in either retinal degenerative diseases and neurodegerative diseases such as for instance, Alzheimer' s disease (AD) or Parkinson's disease (PD), do not significantly differ. Therefore, the drug targets being investigated are similar in both types of diseases.

In this context, we thought of interest to review here three pathogenic features that are common to both neurodegenerative diseases and retina degeneration, that is, excitotoxicity linked to Ca^{2+} dyshomeostasis, oxidative stress associated to mitochondrial dysfunction, and neuroinflammation mediated by the purinergic receptor P2X7 (P2X7R). Based on the therapeutic concept that various chronic diseases are best treated with combined drugs acting on different targets, the concept here raised suggests that novel multi-target therapeutic approaches with orally administered combined triads of repositioned medicines acting on the three above mentioned common pathogenic pathways may delay, slow, or even stop the progression of retina degeneration in glaucoma, DR, AMD and RP, versus single-target drug treatments. We will next review the implication of those three signaling pathways in the pathogenesis of retinal degeneration.

2. Calcium dyshomeostasis, excitotoxicity and retinal degeneration

To better understand the role of distorted Ca^{2+} dynamics in retinal degeneration we will first briefly review the mechanisms involved in the handling of Ca^{2+} by excitable cells and its implication in cell survival and death.

2.1. Calcium homeostasis and neuronal function

At each moment of cell activity, the homeostasis of Ca^{2+} is determined by fluxes between three compartments: the extracellular medium, the cytosol and the Ca^{2+}-storage organelles. At rest, the free Ca^{2+} concentrations are in the range of 10^{-7} M in the cytosol and the mitochondrial matrix, and around 10^{-3} M at the extracellular medium and at

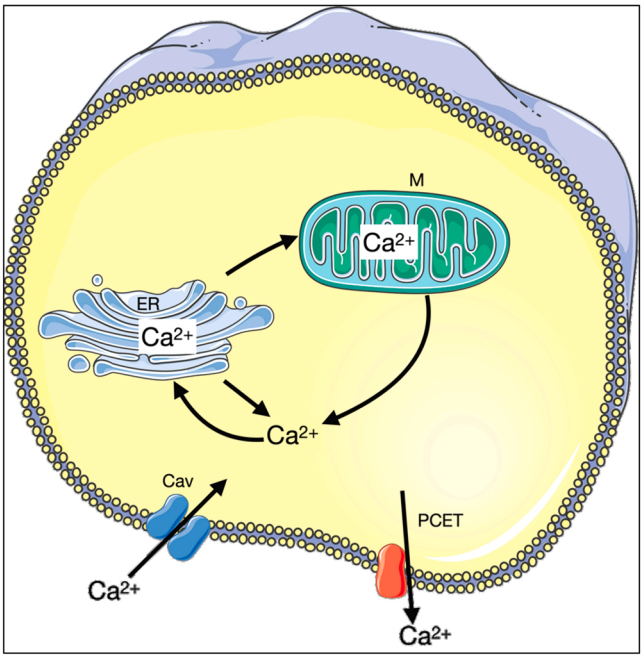

Fig. 2. Intracellular calcium homeostasis. The cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$) at each moment of cell activation is determined by Ca^{2+} fluxes among different cellular compartments, including (i) Ca^{2+} entry through plasmalemmal voltage-dependent calcium channels (Cav) that open during cell activation, (ii) Ca^{2+} sequestration into and Ca^{2+} release from the endoplasmic reticulum (ER) and mitochondria (M), and (iii) plasmalemmal Ca^{2+} efflux transporters (PCET). The ER stores high concentrations of free Ca^{2+} at rest, while it is present at low concentrations in M and cytosol. After cell activation, Ca^{2+} enters into the cytosol through Cav or is released from the ER. The M take up vast amounts of Ca^{2+} either from subplasmalemmal sites and/or from Ca^{2+} released from the ER. http://smart.servier.com/.
Adapted from [8], with images obtained from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Generic License.

the endoplasmic reticulum (ER) store. Consequently, there are huge concentration gradients favoring Ca^{2+} diffusion to the cytosol. Thus, the increase of local cytosolic Ca^{2+} concentrations ($[Ca^{2+}]_c$) is controlled by (i) Ca^{2+} entry through plasmalemmal calcium channels that open during cell activation, (ii) Ca^{2+} sequestration into and Ca^{2+} release from the ER and mitochondria, and (iii) plasmalemmal Ca^{2+} efflux transporters (Fig. 2) [8].

The entry of Ca^{2+} into neurons mainly occurs through ionotropic glutamate receptor channels (i.e. N-methyl-D-aspartate, NMDAR; α-amino-3-hydroxy-5-methylisoxazol-4-propionic acid, AMPAR) and voltage-activated calcium channels (Cav). Upon cell activation, Ca^{2+} ions enter the cell through a 10^4 Ca^{2+} gradient, giving rise to high $[Ca^{2+}]_c$ microdomains (HCMDs) at specific sites [9,10]. The generation of HCMDs may also occur by ER Ca^{2+} release through inositol trisphosphate (IP_3) receptor channels or via ryanodine receptors (RyRs) through Ca^{2+}-induced Ca^{2+} release (CICR) [11].

Calcium transport by mitochondria has received much attention because its three well-defined roles: (i) the shaping of the $[Ca^{2+}]_c$ transients; (ii) the regulation of mitochondrial respiration and ATP synthesis; and (iii) the activation of the programmed cell death [12]. Ca^{2+} is taken up through the mitochondrial Ca^{2+} uniporter (mCU), a low-affinity/high-capacity system [13]; the driving force of the mitochondrial membrane potential (−150 to −180 mV) would promote the accumulation of Ca^{2+} into the mitochondrial matrix up to 5–6 orders of magnitude above the $[Ca^{2+}]_c$ [14]. Ca^{2+} exit from mitochondria takes place through a Na^+/Ca^{2+} exchanger and also through a Na^+-independent system [15]. Plasma membrane Ca^{2+} exit is due to joint operation of a high-affinity Ca^{2+}-ATPase and the Na^+/Ca^{2+} exchange transporter [16].

Finally, cytosolic calcium-binding proteins (CaBPs) with low Ca^{2+} affinity also contribute to the clearance of HCMDs. The brain is rich in CaBPs namely parvalbumin, calbindin-D28K, calmodulin, calcineurin, calretinin, and the S-100 family. Parvalbumin, calbindin-D28K, and calretinin are generally regarded as Ca^{2+} buffering proteins rather than Ca^{2+} regulatory proteins; hence, they play a vital role in neuronal Ca^{2+} homeostasis [17,18]. The expression levels of CaBPs in specific neurons is conditioning the shaping of $[Ca^{2+}]_c$ transients, as well as the Ca^{2+}-dependent vulnerability of those neurons to different types of stressors. For instance, cortical neurons containing calretinin are resistant to calcium overload and excitotoxicity. Furthermore, in tissues from patients with either amyotrophic lateral sclerosis (ALS) or temporal lobe epilepsy, neurons containing calbindin or parvalbumin survive while those lacking them undergo degeneration [19,20].

This complex machinery for the regulation of Ca^{2+} homeostasis is required for multiple Ca^{2+}-dependent functions namely neurotransmitter release [21], short and long-term synaptic plasticity [22] or expression of genes [23]. These functions are exerted by a variety of Ca^{2+} responsive elements, such as proteins involved in synaptic vesicle fusion with the plasmalemma during exocytosis (synaptotagmins), Ca^{2+}-dependent kinases and phosphatases (Ca^{2+}/CaM kinases and Ca^{2+}-dependent phosphatase calcineurin), Ca^{2+}-dependent signaling enzymes (adenylate cyclase and nitric oxide synthase), and Ca^{2+}-dependent transcription factors (cyclic AMP response element binding protein (CREB), calcineurin β-controlled nuclear factor of activated T-cells (NFAT), and Ca^{2+} binding downstream regulatory antagonist modulator (DREAM)). The diversity of these Ca^{2+}-dependent elements provides a means for Ca^{2+}-dependent regulation of neuronal function in a time scale ranging from microseconds (as in the case of vesicle fusion during neurotransmitter release), to seconds and minutes (as in the case of Ca^{2+}-dependent protein phosphorylation and dephosphorylation), to days and years (as in the case of Ca^{2+}-dependent changes in neuronal gene expression). These Ca^{2+}-dependent processes lead to short- and long-term changes in neuronal excitability (by modulating ion channel expression and activity) and synaptic transmission (by modifying the synaptic machinery and facilitating the formation or disassembly of synaptic connections) [24].

2.2. Calcium, neuronal viability and neuronal death

It is intriguing that Ca^{2+} ions may promote cell survival (at lower cytosolic concentrations) or cell death (at higher cytosolic concentrations). This could be explained considering the extreme sensitivity of neurons to variations in Ca^{2+} signals. Thus, even subtle defects and abnormalities in the complex machinery that control the signals might lead to devastating consequences, as in the case of neurodegenerative diseases [25,26].

The role of Ca^{2+} as a death trigger was first suggested by Albrecht Fleckenstein in 1974. He proposed that excess Ca^{2+} influx into cardiac myocytes could be the mechanism underlying the pathology of cardiac ischemia [27]. This concept was extended soon to other tissues showing that both, receptor overstimulation [28] and cytotoxic agents [29,30] induced lethal influx of Ca^{2+} into cells. Additionally, excess Ca^{2+} entry through L-type voltage-activated Ca^{2+} channels (Cav) also elicited mitochondrial disruption and cell death [31]. It is however puzzling that a mild sustained $[Ca^{2+}]_c$ elevation may have opposite neuroprotective effects; this is the case of the rescue of neurons from death by a mild elevation of the extracellular K^+ concentration [32–35]. Also, depolarization preconditioning produced neuroprotection [36]; in this direction are the observations that the K^+ channel blocker tetraethylammonium [37] or blockers of the M-type K^+ current [38] also caused neuroprotection. The mechanism underlying these effects may be linked to cell depolarization, activation of Cav (particularly the L-subtype), and elevation of $[Ca^{2+}]_c$ [39].

The formulation of the interesting hypothesis of the Ca^{2+} set point

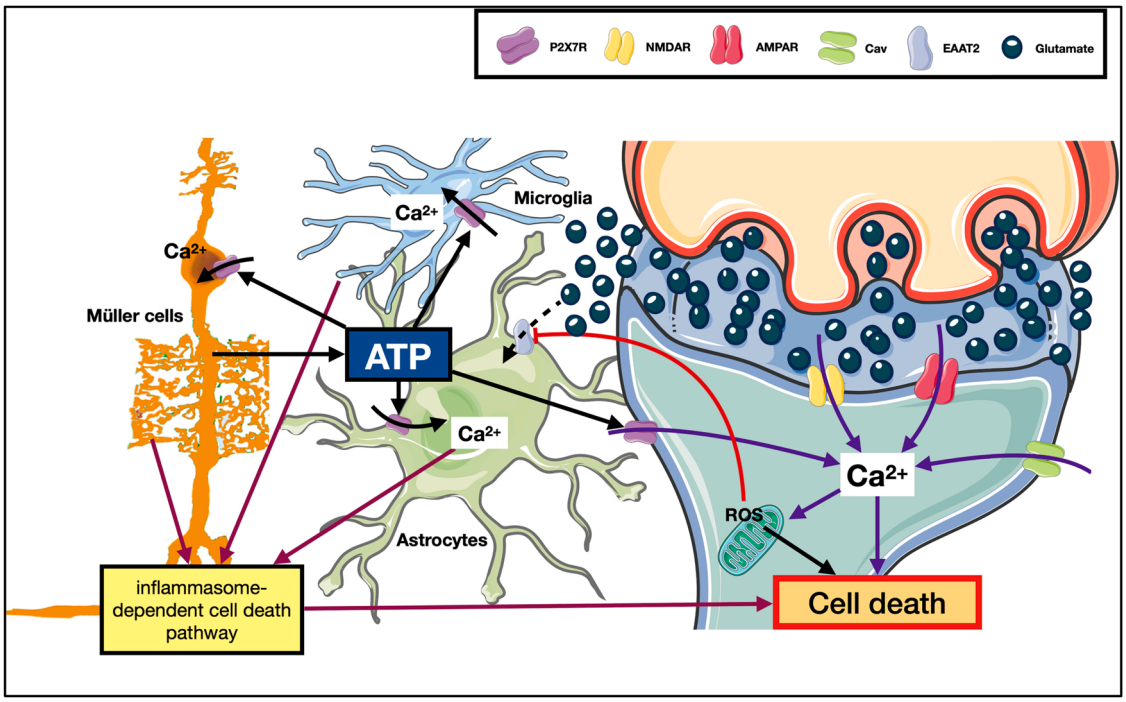

Fig. 3. Plausible pathway of cell death in Ca^{2+}-dependent excitotoxicity. High rate of Ca^{2+} influx through NMDA and AMPA receptors or voltage-activated Ca^{2+} channels (Cav) seems to be the main pathway leading to neuronal injury in excitotoxicity. Enhanced Ca^{2+} entry through the P2X7R pore also elicits Ca^{2+} overload. Elevated intracellular Ca^{2+} induces the activation of cellular enzymes with potential toxic effect, mitochondrial dysfunction, ROS formation and the subsequent death of postsynaptic neurons. Activation of P2X7Rs in glial cells are involved in the inflammasome-dependent cell death pathway. Extracellular ATP released from lesioned neurons or glia causes further activation of microglia leading to the release of pro-inflammatory cytokines, the propagation of gliosis, and cell death. EAAT2, excitatory amino acid transporter 2.
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indicates that a minimal $[Ca^{2+}]_c$ elevation is required to maintain neuronal viability [40]. When the $[Ca^{2+}]_c$ moves below or above this set point, the apoptotic cascade is rapidly activated, leading to neuronal death. This apoptotic effect may involve the transcriptional activation and synthesis of antiapoptotic factors; also, it could be that Ca^{2+} influx keeps the ER Ca^{2+} store filled, thereby preventing its depletion by apoptotic stimuli or ER stress responses [41].

2.3. Calcium and excitotoxicity

Pioneering experiments demonstrated the Ca^{2+}-dependence of glutamate-elicited excitotoxicity [42]. Soon thereafter, this mechanism was linked to several diseases of the nervous system [43] and was considered to be the final common pathway leading to neuronal death in neurotrauma, stroke, epilepsy, and neurodegenerative diseases [44,45].

In the central nervous system, the basal extracellular concentration of glutamate is kept at around 0.6 μM, as monitored by intracerebral microdialysis [46]. Its elevation to 2–5 μM is sufficient to cause excessive glutamate receptor stimulation and neuronal death [47,48]. Physiologically, AMPA receptors mediate fast excitatory neurotransmission while NMDA receptors are responsible for the late component of excitatory neurotransmission [49], playing a key role in synaptic plasticity [50].

Ionotropic glutamate receptors are permeable to Na^+, Ca^{2+}, and K^+ to different degrees, while metabotropic receptors are coupled to G-proteins to control second messenger pathways. Changes in the tetramer subunits may change the Ca^{2+} permeability of ionotropic receptors. For instance, the down regulation of glutamate receptor 2 (GluR2) results in enhanced Ca^{2+} influx through AMPA receptors and enhanced death of vulnerable neurons upon brain ischemia [51]. Also, at postsynaptic levels, energy depletion makes neurons more vulnerable, leading to NMDA receptor-mediated neuronal damage in the presence of normal levels of glutamate [52]. Thus, the excess Ca^{2+} influx through NMDA and AMPA receptors or Cav channels seems to be the main pathway leading to neuronal injury in excitotoxicity [42,53]. The plausible mechanism underlying neuronal death induced by excess Ca^{2+} is schematically presented in Fig. 3.

Excess Ca^{2+} entry causes a sustained elevation of the cytosolic Ca^{2+} concentration, which elicits the activation of protein kinase C, phospholipases, lipases, endonucleases, proteases, protein phosphatases, nitric oxide synthase, or xanthine oxidase. Furthermore, altered mitochondrial Ca^{2+} handling and overproduction of reactive oxygen species are two interacting mechanisms that also contribute to excitotoxic cell death [54,55].

2.4. Calcium dyshomeostasis, excitotoxicity and retinal degeneration

As discussed above, excitotoxic neuronal death occurs as a consequence of excess activation by glutamate of NMDARs and AMPARs, as well as the activation of Cav channels (particularly of the L-subtype); this lead to augmented Ca^{2+} entry, increased $[Ca^{2+}]_c$, mitochondrial Ca^{2+} overload, and apoptosis [56,57]. Various experiments suggest the involvement of Ca^{2+} overload in retinal damage. Thus, prolonged cytosolic and mitochondrial Ca^{2+} overload through these three calcium channels contributes to retinal damage during ischemia [58,59]. This excess Ca^{2+} influx activates the calpain-dependent apoptosis pathway and calcineurin activation in retinal pathologies such as glaucoma or retinitis pigmentosa [60–64].

A few experiments suggest the involvement of the L-subtype of Cav channels in excitotoxicity. So, the blocker nifedipine attenuated the slow excitatory amino acid-elicited neurotoxicity [65]. Additionally, on an in vivo rat model of retinal ischemia, pretreatment with nifedipine

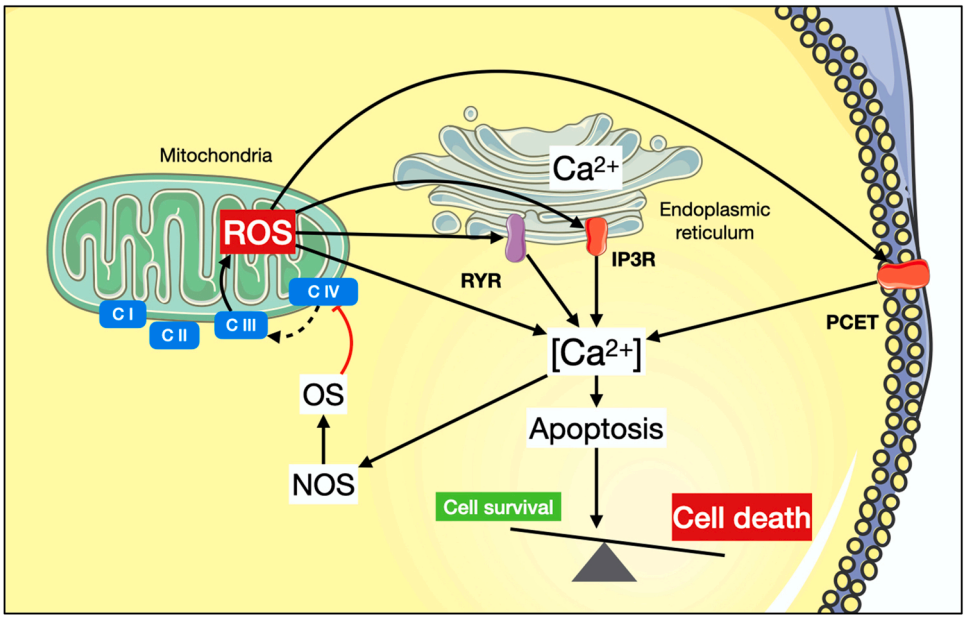

Fig. 4. Link between oxidative stress, mitochondrial calcium handling, and cell death. C I-C IV: mitochondrial complexes I-IV; IP_3R: inositol trisphosphate receptor; NOS: nitric oxide synthase; NO: nitric oxide; PCET: plasmalemmal Ca^{2+} efflux transporters; ROS: reactive oxygen species; RYR: ryanodine receptor. Images modified from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Generic License. http://smart.servier.com/.

facilitated the recovery of the b-wave amplitude of the electroretinogram [66]. Also, Cav channel blockers as diltiazem or nivaldipine have shown neuroprotective effects in animal models of RP [67], although the effects of calcium channel blockers on photoreceptor rescue remain controversial. In murine models, cyclosporine A and NIM811, two inhibitors of the mitochondrial permeability transition pore (mPTP), blocked all Ca^{2+}-induced apoptosis of rod photoreceptors [68]. Furthermore, the topical "wide-spectrum" Cav blocker flunarizine reduced IOP and protected the retina against ischemia-excitotoxicity [69,70]. Flunarizine also decreased Ca^{2+} overload and lipofuscin formation in human RPE cells and maintained cellular vitality, showing its probable clinical relevance in AMD [71].

Brimonidine and other $\alpha 2$ agonists can protect RGCs under disease conditions by preventing abnormal elevations of $[Ca^{2+}]_c$ either in RGCs and/or in their presynaptic cells through the modulation of L-type Cav channel activity [72]. The blocking of Na^+ and Ca^{2+} influx by beta-blockers as timolol and levobetaxolol is also neuroprotective, as shown in a rat model of ischemia/reperfusion [59,73].

RGCs are sensitive to damage elicited by excessive glutamate [74] due to activation of a Ca^{2+}-dependent caspase cascade [75]. The observation that intraocular glutamate levels were increased in glaucoma patients [76] raised the hypothesis that blockade of glutamate receptors could protect RGCs; this was shown to be true in a high IOP model in the rat, using the potent NMDAR antagonist MK-801 [77,78]. On the other hand, the reversible NMDAR antagonist memantine afforded robust neuroprotection against glutamate toxicity in RGCs [75, 79]. Furthermore, the peptide somatostatin has a neuroprotective role in the retina against glutamate-induced neurotoxicity and ischemia [80]. Some studies have shown that the activation of somatostatin receptors may protect RGCs by the suppression of T-type Ca^{2+} currents and the intracellular NO/cGMP/PKG signaling pathway [81]. Moreover, somatostin can regulate intracellular Ca^{2+} levels via L-type Cav channels [82].

Evidence also points to the involvement of transient receptor potential (TRP) calcium channels in retinal degeneration, first shown in experiments in *Drosophila* [83] and then in mammals, due to their relationship with Ca^{2+} homeostasis [84]. In glaucoma, the exposure of retinal ganglion cells to elevated pressure can induce an increase of intracellular Ca^{2+} accumulation due to activation of transient receptor potential vanilloid 1 (TRPV1) and 4 (TRPV4) channels, what leads to apoptosis of RGCs [85–87]. Thus, high extracellular levels of glutamate and the increased Ca^{2+} entry through NMDARs, AMPARs, Cav channels and TRPV4 channels influence the RGC death [88,89].

An activated unfolded protein response (UPR) and mitochondrial dysfunction characterize the pathology of autosomal dominant RP in rat models. The sustained UPR in the wild-type retina can promote retinal degeneration through increased intracellular Ca^{2+} and Ca^{2+}-mediated calpain activation [90,91]. Other studies suggest that Ca^{2+} accumulation activates photoreceptor death by caspase-dependent apoptosis. Thus, in degenerating photoreceptors of the rd1 model of RP, enhanced intracellular accumulation of Ca^{2+} was accompanied by augmented calpain activation and apoptosis; congruent with this, calcium channel blockers decreased calpain activation and apoptosis both in vitro and in rd1 mice, suggesting that elevated Ca^{2+} is required for calpain activation and calpain-induced cell-death [92]. In this context, another study showed that inhibition of calpain reduced photoreceptor death in the rd10 mouse model of RP [93].

Concerning DR, it is known that hyperglicemia is a major risk factor for endothelial dysfunction and vascular disease in diabetic patients. High glucose levels in diabetic patients can influence the influx of Ca^{2+} in endothelial cells, with an impact on Ca^{2+}-induced cell death. Some experiments have shown that high glucose levels can increase Ca^{2+} entry, as that induced by ATP in bovine aortic endothelial cells by enhancing the expression of transient receptor potential canonical 1 (TRPC1) channels [94]. In the macaque cell line RF/6 A of choroid-retinal endothelial cells cultured in hyperglycemic conditions, Ca^{2+} entry activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which contributes to cell apoptosis by activating both Fas-dependent and mitochondria-dependent apoptosis pathways [95].

In summary, evidence supporting the view that neuronal (and mitochondrial) Ca^2 overload lead to apoptotic cell death is overwhelming. In the case of the retina, evidence is accumulating proving that Ca^{2+} overload is also a pathogenic feature in various experimental models of retinal degeneration and hence the pharmacological mitigation of such Ca^{2+} overload could drive retinal protection.

3. Oxidative stress, mitochondrial dysfunction and neurodegeneration

Again, to better understand the implication of excess oxidative stress in retinal degeneration, we will briefly comment on its concept and link with distorted mitochondrial Ca^{2+} handling and its role in neuronal death. Then, these concepts will be extrapolated to retinal degeneration.

3.1. Oxidative stress

The concept of oxidative stress has its origin in the pioneering observation that patients with hematological diseases had defective glutathione reductase [96]. Later on, it was demonstrated that in isolated heart mitochondria, the respiratory chain was capable of producing superoxide anion and indirectly hydrogen peroxide [97]. Afterwards, oxidative stress was defined as an imbalance between the biochemical reactions that generate reactive oxygen species (ROS) and those responsible for their removal.

In mammalian cells, ROS are generated in mitochondria, endoplasmic reticulum, cytosol, and the extracellular space. In mitochondria, the most active sites for ROS production are complex I and complex III of the oxidative phosphorylation chain [98]. Mitochondria are not only the major source of ROS; they are also particularly vulnerable to ROS-inflicted damage, particularly mitochondrial DNA. This damage has detrimental functional consequences with excess ROS production and decreased ATP synthesis; this results in bioenergetic failure thereby limiting the energy available for key cellular processes such as neurotransmitter release and repair after tissue injury. This explains that mitochondrial dysfunction contributes to the pathogenesis of neurodegenerative diseases [99] and optic neuropathies [100].

3.2. Link between oxidative stress, distorted mitochondrial calcium handling and neuronal death

Conditions that provoke oxidative/nitrosative stress results in Ca^{2+} overload and neuronal death [101,102] (Fig. 4). ROS are generated as byproducts of the mitochondrial respiratory chain [103]. On the other hand, there is a positive correlation between the Ca^{2+}-dependent metabolic rate and ROS production [104]. Furthermore, Ca^{2+} stimulates nitric oxide (NO) by NO synthase (NOS) which blocks complex IV leading to ROS production in complex III [105]. Conversely, ROS regulate several Ca^{2+} transporters and signaling proteins of the mitochondria-endoplasmic reticulum communication system [106]. ROS also modulate ryanodine receptors [107] and IP_3 receptors (IP_3Rs) as well as plasmalemmal and ER Ca^{2+} transporters [105] thus contributing to elevated $[Ca^{2+}]_c$ during oxidative stress. Therefore, in neurodegenerative diseases mitochondrial dysfunction is associated to four interacting pathways namely, altered Ca^{2+} homeostasis, excessive ROS production, induction of apoptosis, and neuronal death [101,102,108,109].

3.3. Oxidative stress and retinal degeneration

Augmented oxidative stress has been implicated in various eye diseases leading to retinal degeneration. In glaucoma patients, NOS and nitrotyrosine are augmented in the trabecular meshwork, which is responsible for draining the aqueous humor in the anterior eye chamber [110]. RGCs are highly sensitive to excess oxidative stress linked to mitochondrial dysfunction in glaucoma [111]. Also, apoptotic RGC death is directly linked to high intraocular pressure; in its turn, death of RGCs increases ROS, leading to optic nerve retinopathy. The influence of mitochondrial misbalance and ROS in the development of the neurodegenerative process is crucial from the early stages of the disease [112–114].

Oxidative damage also contributes to both, the onset and progression of AMD [115,116] and accounts for the main pathological manifestations, including the dysfunction of RPE and breakdown of the blood retinal barrier [117,118]. During ageing, oxidized polyunsaturated fatty acids (PUFAs) are not efficiently digested and are deposited in RPE cells in the form of lipofuscin, a chromophore involved in ROS formation. Furthermore, cones, which are highly sensitive to free radicals and are the predominant photoreceptors at the macula, have a high demand of oxygen and also contribute to ROS production. With age, the DNA repair system and antioxidant defences decrease, contributing to the increase of accumulated damage [115]. The high local oxygen exposure, together with lifestyle choices as smoking, sunlight exposure or diet leads to oxidative damage in AMD [116]. Many preclinical studies in animal models of AMD have shown a protective effect of antioxidant substances as resveratrol, carotenoids and omega-3 fatty acids (reviewed in [119]).

ROS also contribute to DR initiation and progression. Oxidative stress is a key factor as indicated by the observation that hyperglycemia induces mitochondrial overproduction of such stress [120,121]. With the antioxidant defences impaired in DR, ROS are increased first by the increase of oxidized glucose and mitochondrial overproduction of ROS, but also via other metabolic pathways namely the polyol pathway, the advanced glycation end product (AGE) pathway, and the protein kinase C (PKC) pathway, which have key repercussions in the pathogenesis of DR [120,121].

Oxidative stress has also a main role in inherited retinal degenerative processes; it is increased in the outer retina of RP animal models and in the ocular samples of RP patients. On the other hand, anti-oxidant interventions delay photoreceptor cell death in experimental RP [122]. Also, DHA has shown protection in murine models of light damage [123,124]. After the rod cell death, oxygen consumption is reduced in RP retinas, resulting in high tissue levels of oxygen in the outer retina. Then, cones exposed to high levels of tissue oxygen begin to degenerate. As oxidative stress spreads, cones dye from the periphery to the central zone of the retina, decreasing the area of surviving cones and diminishing the remaining visual field, ending at the macula, which is the area of highest cone cell density [125]. Furthermore, the oxidative damage is directly involved in microglia activation and the neuroinflammatory process, and anti-oxidant treatments can suppress the activation of microglia [122]. In line with this is a study done in the rd10 mouse model of RP; antioxidants reduced inflammatory markers, suggesting that oxidative stress contributes to the induction of apoptosis [126].

In summary, oxidative stress is a relevant pathogenic pathway leading to neuronal cell death in neurodegenerative diseases; similarly, oxidative stress is implicated in retinal degeneration in the four eye diseases here analyzed. The pharmacological mitigation of oxidative stress rescues retinal cells from death in several cell and animal models of disease.

4. Neuroinflammation linked to P2X7 receptors and retinal degeneration

Neuroinflammation associated to glial activation is implicated in practically all neurodegenerative diseases and also in retinal degeneration. We will briefly review this general topic to better understand its introduction in the field of retinal damage.

4.1. The P2X7R as a gatekeeper of inflammation

The concept of purinergic signaling mediated by ATP and purinergic receptors arose about 50 years ago [127]. Purinergic receptors are classified as P1 and P2; they are activated by adenosine and ATP, respectively. P2Y receptors are metabotropic and $P2X_{1-7}$ receptors are ATP-gated ion channels permeable to Na^+, Ca^{2+}, and K^+, and to larger molecules up to 1 kDa [128–131]. P2X7Rs activation triggers IL-1β release and is involved in macrophage communication and differentiation [132,133]; this led Francesco di Virgilio to formulate the proposal that P2X7Rs are acting as mediators of chronic inflammatory responses

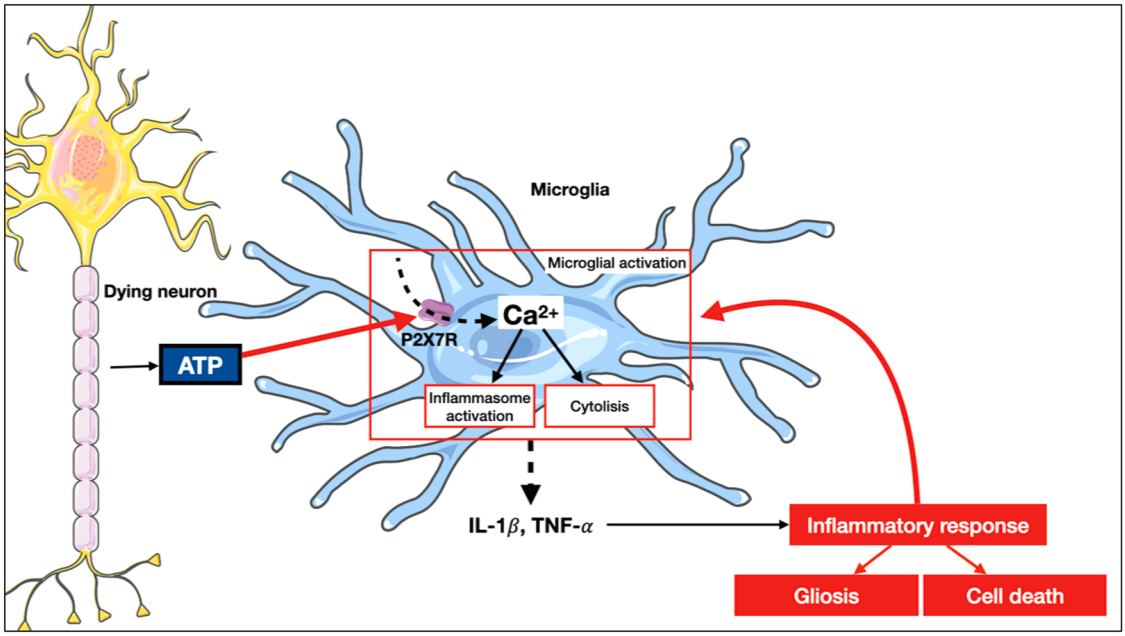

Fig. 5. Implication of P2X7Rs in brain neuroinflammation. ATP released from dying neurons activate P2X7Rs, with intracellular Ca^{2+} overload, inflammasome activation and cytolysis. The release of proinflammatory cytokines as TNF-α and IL-1 which promotes further microglia activation, gliosis and cell death. Original images were obtained and modified from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Generic License. http://smart.servier.com/.

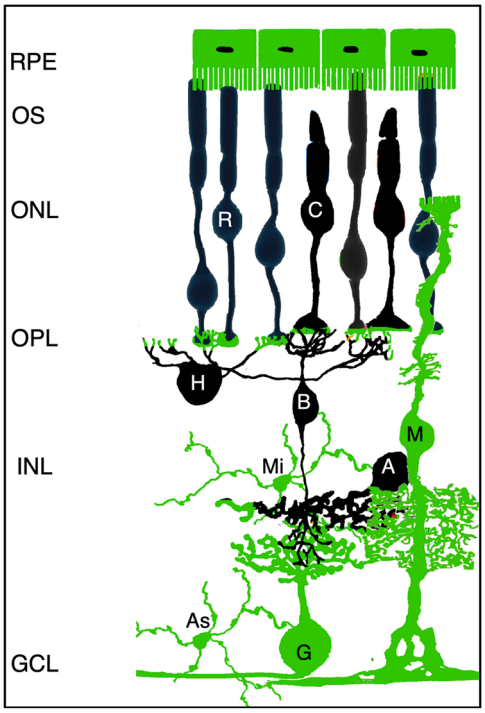

Fig. 6. Cells expressing P2X7Rs in the mammalian retina. P2X7Rs are expressed in retinal pigment epithelial cells (RPE), retinal ganglion cells (G), Müller cells (M), microglia (Mi) and astrocytes (As), as well as in the synaptic ribbons of rods (R), cones (C), horizontal (H) and amacrine cells (A), shown in green. RPE, retinal pigment epithelial cell; OS, outer segments; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; GCL, ganglion cell layer; B, bipolar cells.

[133,134]. The concept is supported by the fact that P2X7Rs are expressed in immune and inflammatory cells such as dendritic cells, osteoclasts, mast cells, natural killer cells, and T and B lymphocytes [131].

The implication of P2X7Rs in brain neuroinflammation is supported by their expression in astrocytes and microglia, where they activate the inflammasome. The assembly of the NLRP3 inflammasome complex in microglia is elicited by P2X7R activation by the high ATP concentrations released from damaged neurons; as a result, the secretion of pro-inflammatory cytokines such as IL-1β takes place [135,136] (Fig. 5).

4.2. P2X7Rs, neuroinflammation and retinal degeneration

P2X7Rs are abundantly expressed in several types of retinal cells such as astrocytes, microglia, Müller cells, RPE, or pericyte-containing microvessels [137–139]. They are also expressed in neuronal type cells, including RGCs, horizontal and amacrine cells of the inner nuclear layer, the outer plexiform layer (synaptic sites of rods and cones), and the inner plexiform layer [139–141] (Fig. 6).

Through the physiological activation of ionotropic P2X7Rs, ATP contributes to fast excitatory transmission in the retina [142,143]. This is in line with the observation that P2X7R activation elicits changes in the a- and b-waves of the electroretinogram (ERG) as well as in the oscillatory potentials [139,144–146].

P2X7Rs also play a prominent role in retinal gliosis and retinal degeneration. through two mechanisms: excessive Ca^{2+} entry through the P2X7R pore elicits (i) Ca^{2+} overload and cytolysis [147]; and (ii) activation of the inflammasome-dependent cell death pathway[148]. Excess ATP release from lesioned neurons or glia causes the further activation of microglia, leading to the release of pro-inflammatory cytokines IL-1β and TNF-α this promotes further microglia activation, the propagation of gliosis, with secondary cell death [149,150], and the progression of retinal degeneration [3,148] (Fig. 5). The activation of microglia and the implication of P2X7Rs has been shown to occur in models of retina damage induced by elevated IOP. In a rat model of chronic ocular hypertension, excessive ATP release was accompanied by RGC damage linked to P2X7Rs; by shifting purinergic balance and blocking P2X7Rs, inhibition of microglial activation and protection of RGCs was observed [150]. In another study, the pressure-induced damage of RGCs was prevented by P2X7R blockade, indicating once more the implication of this receptor in glaucoma [151] and the potential of P2X7R blockers as pharmacological protecting targets in the

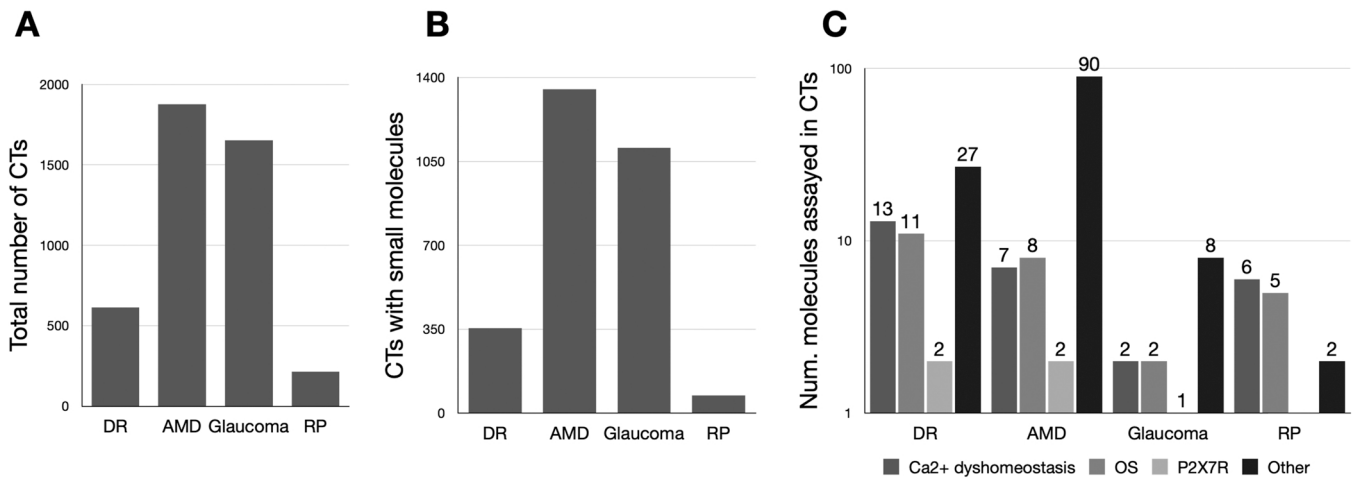

Fig. 7. Number of clinical trials found in the FDA database ClinicalTrials.gov, done in patients with diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, and retinitis pigmentosa (RP). A, total number of clinical trials (CTs). B, CTs with small molecules. C, CTs with small molecules that target Ca^{2+} dyshomeostasis/excitotoxicity, oxidative stress (OS), P2X7Rs activity-linked neuroinflammation (P2X7R) or other targets outside the scope of this review.

disease. Other studies have shown the activation of microglia, and hence, the presence of neuroinflammation in this disease [152]. In a mouse model of chronic glaucoma with early microglia activation, anti-inflammatory microglia improved optic nerve integrity and reduced retinal microglial activation [153]. Also, high IOP induced the upregulation of retinal GFAP and MHC-II, as well as microglia reactivity in mice retina [154] and reactive nonproliferative gliosis in a mouse model of glaucoma [155]. Glial toll-like receptors (TLRs) have also been implicated in stressed glaucomatous tissue [156]. Increased secretion of inflammatory proteins such as TNF-α from glaucomatous tissues and upregulation of their expression [152] is congruent with the observation that inhibition of reactive microglia with anti-inflammatory minocycline augmented RGC survival [157,158]. In this frame, the inhibition of signaling cascades such as NO synthase or TNF-α initiated in reactive microglia, are potential therapeutic strategies in glaucoma [158–160]. Minocycline has also shown protection against inflammation-induced photoreceptor cell death in murine models of inherited retinal degeneration [161] and light damage[162,163]. Furthermore, as in the human disease, immunostimulatory signaling can also be triggered by glial TLRs; this could also become another therapeutic target.

In AMD, calcium dyshomeostasis can be mediated through the activation of P2X7Rs, that could cause the dysfunction and apoptosis of RPE. Yang et al. (2011) showed that in human RPE cells both the non-selective endogenous agonist ATP and the selective P2X7R agonist 2,3-O-(4-benzoylbenzoyl)-ATP (BzATP) can increase intracellular Ca^{2+} via extracellular Ca^{2+} influx and induce apoptosis. This Ca^{2+} increase was significantly inhibited by the P2X7R antagonist oxidized ATP (oATP) but not by the P2 receptor antagonist suramin, inhibited by BAPTA-AM and also by low extracellular Ca^{2+} [164]. P2X7Rs are expressed in the RPE and different layers of the retina and are functional both in vitro and in vivo, thus mediating AMD-like defects [165]. P2X7Rs expressed in microglia and macrophages normally function as scavenger receptors; so, functional alterations in this process can predispose individuals to AMD [166]. Moreover, one of the main components of lipofuscin is the bisretinoid N-retinyl-N-retinylidene ethanolamine (A2E), which cannot be enzymatically degraded, and it is accumulated in aged RPE cells. On the other hand, microglial cells in culture can internalize A2E and change it into an activated pro-inflammatory phenotype [167].

Concerning DR, it is notable that elevated glucose levels increase the extracellular ATP concentration, which activates the P2X7 receptors (P2X7Rs) and evokes the release of proinflammatory cytokines IL-6, TNF-α, and CCL2 in primary microglia [168]. In DR, purinergic-elicited vasotoxicity influences the death of microvascular pericytes and endothelial cells [169]. In a rat model of diabetes induced by streptozotocin, it was shown that P2X7R antagonists caused the reversion of increased vascular permeability, VEGF accumulation, and IL-6 expression [170]. In diabetic retinas, Müller cells show an increased expression of CD40 and P2X7Rs. CD40 ligation causes phospholipase C-γ1 (PLC-γ1) activation, and secretion of extracellular ATP by Müller cells, which binds to P2X7Rs leading to secretion of TNF-α and IL-1β. The CD40-ATP-P2X7R pathway is linked with the programmed cell death of bystander retinal endothelial cells, what likely contributes to degeneration of capillaries [171].

Inflammation also has a central role in RP. In fact, infiltration of the degenerating regions of the retina by microglia and blood-derived macrophages is present in rd1 and rd10 retinal degeneration mice as well as in post-mortem samples from RP patients [172–174]. Accordingly, P2X7Rs also seem to have a role in RP. In this sense, the intravitreal injection of the purinergic antagonist pyridoxal-phosphate-6-azophenyl-2,4-disulfonic acid (PPADS) protected against ATP-mediated apoptosis in rats with intravitreal injection of high concentrations of ATP. This antagonist also increased the photoreceptor survival in the rd1 mouse [175].

In summary, both in neurodegenerative diseases and in retinal degeneration neuroinflammation mediated by P2X7R activation is a major cause of neuronal death and retinal cell damage; thus, in some studies the pharmacological blockade of P2X7Rs rescue retinal cells from death in various models of eye diseases. This suggests that this receptor is a good target to develop antagonists with potential neuroprotective effects in eye diseases leading to retinal degeneration.

5. Pharmacological targets addressed in clinical trials in patients with eye diseases that lead to retinal degeneration

In a search of clinical trials (CTs) at the US Food and Drug Administration (FDA) database ClinicalTrials.gov, the total number of registered studies are as follows: DR 611, AMD 1346, glaucoma 1099, and RP 178 (Fig. 7A) [176]. Some studies are done with large molecules genetic approaches. Many others are done with small molecules: 350 in DR, 1380 in AMD, 1060 in glaucoma, and 20 in RP (Fig. 7B). The number of small molecules directed to targets linked to the three pathogenic pathways of retinal degeneration here discussed (calcium dyshomeostasis, oxidative stress, and neuroinflammation) are considerably smaller (Fig. 7C). Thus, in DR, AMD, and RP there are 13, 7 and 6 studies addressing Ca^{2+} dyshomeostasis respectively. Targets associated to oxidative stress are present in 11, 8 and 5 studies in DR, AMD and RP respectively. On the other hand, the number of CTs addressing

Table 1
Main pharmacological targets in clinical use or under evaluation in the treatment of glaucoma, AMD, DR and RP and example drugs.

Disease	Targets	Drug
Glaucoma	β-adrenergic blockers	Timolol
	α2-adrenergic agonists	Brimonidine
	Cholinergic agonists	Pilocarpine
	Prostaglandin analogs	Latanoprost
	Carbonic anhydrase inhibitors	Brinzolamide
	Rho-kinase inhibitors (under evaluation)	Riparsudol
	Adenosine receptor agonists (under evaluation)	Trabodenoson
	Modified prostaglandin analogs (under evaluation)	Latanoprostende bunod
	Combined antioxidants (under evaluation)	α-tocoferol, Vitamins A, B, E, *Ginkgo biloba*
AMD	Anti-vascular endotelial growth factor (VEGF) therapy, sometimes combined with corticosteroids (dexamethasone)	Antibodies: ranibixumab Antibody fragments: brolucizumab Fusion proteins: conbercept
	Antibodies anti-Angiopoietin-2 (under study)	Faricimab
	Anti-Platelet derived growth factor (under study)	Pegpleranib
	Antibody anti-sphingosine-1-phosphate (under study)	Sonepcizumab
DR	Corticosteoids	Triamcinolone
	Antioxidants, monotherapy or in combination (under study)	Combination of lutein, α-tocoferol, β-carotene, niacin, ascorbic acid, zinc, selenium, copper, and manganese
RP	Dietary supplements with antioxidants (under study)	DHA, Vitamin A

Table 2
Examples of successful drug repositioning. The generic drug name is shown together with the original indication, the new indication that arose from repositioning programs, and the reference.

Drug	Original indication	New Indication	Reference
Amantadine	Influenza	Parkinson's disease	[236]
Aspirin	Pain, fever, inflammation	Coronary artery disease	[237]
Amphotericine B	Fungal infections	Leishmaniasis	[238]
Bromocriptine	Parkinson's disease	Diabetes mellitus	[239]
Bupropion	Smoking cessation	Depression	[240]
Celecoxib	Osteoarthritis, reumathoid arthritis	Breast and colon cancer	[241]
Duloxetine	Depression	Urinary incontinence	[242]
Finasteride	Prostatic hypertrophy	Male androgenic alopecia	[243]
Fluoxetine	Depression	Premenstrual dysphoria	[244]
Galantamine	Recovery from curare in anesthesia	Alzheimer's disease	[245]
Gemcitabine	Viral infections	Cancer	[246]
Methotrexate	Cancer	Reumathoid arthritis, psoriasis	[247]
Minoxidil	Hypertension	Male androgenic alopecia	[248]
Paclitaxel	Cancer	Prevention of coronary restenosis	[249]
Raloxifene	Prostate and breast cancer	Postmenopausal osteoporosis	[250]
Ropinirole	Hypertension	Parkinson's disease	[251]
Sildenafil	Chest angina	Erectile dysfunction	[252]
Thalidomide	Hyperemesis gravidarum	Multiple myeloma	[253]
Topiramate	Epilepsy	Binge eating disorder associated with obesity	[254]
Zidovudine	Cancer	AIDS	[255]

neuroinflammation linked to P2X7Rs are scarcely represented, i.e. 2 studies in each DR or AMD. In glaucoma, only 2 studies addressing oxidative stress or Ca^{2+} dyshomeostasis were found. Therefore, most studies in DR (27), AMD (90), glaucoma (8), and RP (2) address other targets. We next comment on CTs and drug targets addressed in glaucoma, AMD, DR, and RP. Main targets and drugs in clinical use or under development are summarized in Table 1.

5.1. Clinical trials and drug targets in glaucoma

Topical drug options for the lowering of IOP in glaucoma include beta-adrenergic blockers (timolol), alpha-2 adrenergic agonists (brimonidine), cholinergic agonists (pilocarpine), prostaglandin analogs (latanoprost), or carbonic anhydrase inhibitors (brinzolamide); these drugs act either by increasing aqueous humor outflow and/or by decreasing its production. Several large, controlled, and randomized CTs have demonstrated the efficacy of reducing IOP to prevent glaucoma development from ocular hypertension [177] as well as disease progression in patients with established glaucoma [178]. One meta-analysis summarized 28 CTs of topical monotherapy for glaucoma [179] and a second one analyzed 41 CTs of fixed drug combinations for topical treatment of glaucoma [180]. More recently, novel candidates for treatment of primary open-angle glaucoma are being developed in clinical trials; some of them are rho kinase inhibitors (ripasudol, netarsudil, AMA0076, AR-12286, DE-104, SNJ-1656), adenosine receptor agonists (trabodenoson), and modified prostaglandin analogs (latanoprostene bunod, ONO-9054) [176,181,182].

Guidelines by the American Academy of Ophthalmology recommend the use of adrenergic beta-blockers and prostaglandin (PG) analogs as first-line treatment of high IOP. This is not always effective in attenuating disease progression in glaucoma. Thus, other drugs acting directly on the optic nerve and on the process of retinal degeneration can provide additional protection [183].

Adrenergic alpha-2 receptors are located both in ciliary processes and RGCs. These are the major cell types affected in glaucoma, and thus, the α2 agonist brimonidine seems to produce both lowering of IOP through reduction of aqueous humor formation and neuroprotection by acting on α2 receptors at RGCs [184]; in fact, one CT found less visual field loss with brimonidine compared with timolol [185]. But the effects of brimonidine also include the upregulation of brain-derived neurotrophic factor expression, inhibition of glutamate release, modulation of NMDA receptors, and regulation of cytosolic Ca^{2+}, that probably accounts for its final effect. In this sense, targeting of NMDA receptors has been another strategy to treat glaucoma patients. However, the reversible NMDAR antagonist memantine failed to demonstrate a significant effect on disease progression (cited by [183]).

CTs with combined antioxidants (mainly polyphenol derivatives) reported some benefits in glaucoma. This was the case of mexidol®, α-tocoferol, or combined vitamins A, B, and E (reviewed by [186]). *Ginkgo biloba*, that exhibits vasoregulatory, neuroprotective, and antioxidant effects can be found in up to 8 CTs, alone or in combination with antioxidants as α-tocopherol [176].

In summary, most CTs and therapeutic strategies in glaucoma are directed towards the reduction of IOP and very few studies focus on direct pharmacological protection of the retina in patients with glaucoma.

5.2. Clinical trials and drug targets in age-related macular degeneration

Most therapies in AMD focus on the blockade of the proliferation and survival of subretinal neovascular membranes [187]. This is achieved through the intravitreal administration of monoclonal antibodies against vascular endothelial growth factor (anti-VEGF). Three of them are in clinical use, namely ranibizumab, bevacizumab, and aflibercept. Intravitreal implants of the corticosteroids dexamethasone and triamcinolone are also used as adjunct treatments, combined with anti-VEGF.

These medications have shown to be safe and efficacious to reduce severe visual impairment. Despite this, many patients continue losing vision, impairing their abilities to read, drive and perform daily

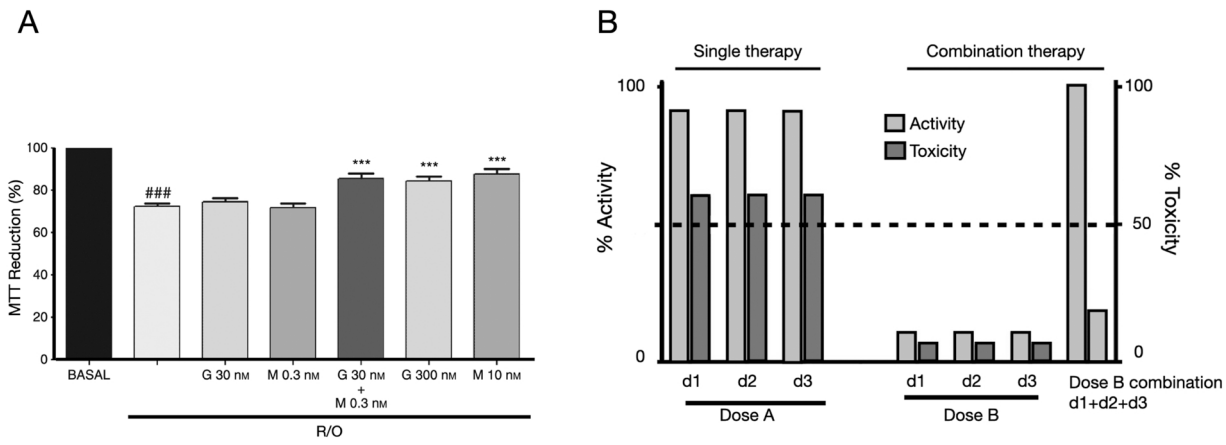

Fig. 8. An in vitro experimental example and a scheme on the synergic effects of drug combinations. A, cell death elicited by oxidative stress of mitochondrial origin, by exposing SH-SY5Y cells to combined rotenone plus oligomycin (R/O). Cell viability (MTT reduction in %, ordinate) showed a 30% cell loss. Neither galantamine (G) nor melatonin (M) at low concentrations, elicited neuroprotection. However, the combination of both drugs exerted a significant neuroprotection. B, scheme showing the desired pharmacological activity and the toxic effect of high drug concentrations (left) of three drugs (d1, d2, d3) and the synergistic effects of activity, but not on toxicity, of combined drugs 1, 2 and 3 at lower concentrations (right).
(A) Adapted from [259]. (B) Adapted from [261].

activities [188]. Furthermore, the therapeutic regimens are cumbersome as due to the relatively short half-life of anti-VEGF, repeated intravitreal injections have to be done monthly. This requires frequent visits to the hospital with concomitant loss of time and productivity [189]. Thus, new therapies are needed for neovascular AMD [190].

Various approaches that are being investigated mostly have the VEGF (and other secondary growth factors) as drug targets. The objective is related to the extension of the half-life of anti-VEGF so that the therapeutic regimen can be reduced to, for instance, quarterly intravitreal injections of anti-VEGF. This was the case of conbercept, a VEGF trap-like molecule that blocks all isoforms of VEGF-A, VEGF-B and VEGF-C [191]. Of interest is brolucizumab, a single-chain antibody fragment that inhibits VEGF-A; it displays similar efficacy than other anti-VEGF but injection frequency is also quarterly [192].

Other drugs acting at different but complementary targets to VEGF are also in clinical development. This is the case for the anti-platelet derived growth factor (anti-PDGF) pegpleranib, combined with anti-VEGF; however, results of a phase III CT gave disappointing outcomes [193]. Another target tested was angiopoietin 2 (Ang-2); faricimab is an antibody that binds to Ang-2 and VEGF-A. A phase II CT with 12- and 16-weeks regimens compared well with monthly treatment with ranibizumab, as far as efficacy was concerned [194]. Of note is an ingenious device to release ranibizumab by passive diffusion from a refilled device, surgically-implanted in the pars plana of the eye. A phase II CT demonstrated that patients with the so-called port delivery system (100 mg/ml) showed visual outcomes comparable to those of monthly 0.5 mg ranibizumab; 79.8% of the patients did not require a refill for 6 months [195].

An alternative target being explored is sphingosine-1-phosphate (S1P) that induces significant capillary formation, acting as a pro-angiogenic factor that directly interacts with other growth factors including epidermal growth factor (EGF) and VEGF receptors. Thus, a monoclonal antibody raised against S1P may be an effective therapy for AMD [196]. Furthermore, reverse transcriptase inhibitors that block the inflammasome and abort the inflammatory process, are also being explored [197]. Gene therapy based in the intravitreal injection of adenovirus carrying a gene expressing a VEGF inhibitory protein has shown limited efficacy so far [198]. Worth mentioning are some studies on inhibitors of tyrosine kinases such as valatanib and pazopanib that do inhibit VEGF receptor subtypes. However, CTs have given negative outcomes [199]. Finally, RNA interference to silence VEGF-A messenger RNA is also being investigated.

Concerning other therapeutic strategies, only a few CTs have assayed molecules with antioxidant properties, some of them also with effect on cytosolic Ca^{2+} modulation, as α-lipoic acid, the antibiotic doxycycline, the immunosuppressant rapamycin or the vasodilator MC-1101, which has also an anti-inflammatory and antioxidant profile. Molecules with multiple mechanisms of action as metformin or brimonidine have also been assayed in CTs to test their neuroprotective potential.

In summary, all therapeutic strategies being applied to patients with AMD, and many other that are in clinical development, focus on the mitigation of the macular neovascularization, mostly by suppressing growth factors with specific monoclonal antibodies intravitreally applied, particularly anti-VEGF antibodies. Targets on retina cells themselves to afford retinal cell protection are scarcely being investigated.

5.3. *Clinical trials and drug targets in diabetic retinopathy*

In trying to delay DR onset and to mitigate disease progression once diagnosed, ophthalmologists do give priority to the adequate control of diabetes mellitus (DM); therapy focus on control of blood glucose and lipids as well as blood pressure, with diet and specific medications [200]. Once diabetes is stabilized, DR treatment is based in standard therapies such as photocoagulation, vitrectomy, or intraocular injections of corticosteroids or anti-VEGF monoclonal antibodies. However, some patients are resistant to these treatments, and hence they suffer DR progression [112]; this has been associated mainly to oxidative stress [201]. Thus, complementary therapeutic approaches focusing on the rebalance of excess free radical production and/or restoration of antioxidant natural systems, have been and are being tested in CTs. Both specific single antioxidant compounds or various antioxidants given in combination are tested [112]; also, diet/nutraceutical supplementation is being studied [202].

A recent comprehensive review comments on 31 CTs done in patients with DR; those studies have been performed with single antioxidant compounds or with combined antioxidant therapy (CAT) [112]. In spite of the large heterogeneity of studies (dosing, use of single antioxidant or CAT, treatment duration), some positive outcomes emerged. For instance, a long-lasting study (5 years) evaluated the effect of CAT (lutein, alpha-tocopherol, niacin, beta-carotene, ascorbic acid, zinc, selenium, copper, and manganese) in 105 patients with DM2 and non-proliferative DR. Authors found a retardation of DR progression but no effect on visual acuity; the antioxidant plasma status was maintained [203]. Another CT with a complex CAT formula (18 antioxidant ingredients!) showed improved visual acuity but no changes in retinal

Table 3
Small molecules that have been, or are being tested individually in clinical trials, acting on one of the three common pathogenic pathways of neurodegenerative diseases and retinal degeneration: calcium overload/NMDARs-AMPARs/Cav channels/excitotoxicity, mitochondrial dysfunction/oxidative stress, and neuroinflammation/microgliosis/P2X7Rs. AD: Alzheimer disease; ALS: amyotrophic lateral sclerosis; AMD: age-related macular degeneration; CT: clinical trial; GA: geographic atrophy; MS: multiple sclerosis; PD: Parkinson disease; RP: retinitis pigmentosa.

Pathogenic pathway	Small molecule	Mechanism of action	References
Calcium overload / NMDA-AMPA receptors-Cav channels/ excitotoxicity	Brimonidine	Blocks NMDA receptors; decreases intracellular Ca^{2+}.	[270] Neuroprotective effects in RP patients, after topical administration
	Cannabis (cannabidiol: THC, 1:1)	Inhibits L-type calcium channels, TRPV1, TRPA1 (activates and desensitizes TRP)	[271] Early phase I CT for RP. Well tolerated by most patients
	Ceftriaxone	Reduces glutamatergic hyperactivity.	[176,272] Phase III CT in ALS
	Curcumin	Modulates HVGCC, CRAC, VGCC (Cav2.2, Cav 2.1). Blocks Ca^{2+} channels. Blocks Ca^{2+} mobilization	[273–278] Well tolerated. Poor bioavailability. Low bioavailability, which can be increased with several formulations, as well as safety, tolerability, and efficacy. Phase II CTs in AD. Phase I CTs for AMD, Phase II in combination with resveratrol and quercetin
	DHA	Reduces endothelial calcium influx.	[216,279,280] Phase II CT in RP. No effects in slowing RP progression were detected
	Empagliflozin	Reduces calcium dysregulation; reduces Ca^{2+}/ calmodulin-dependent kinase II	[281] May prevent preclinical DR with metformin
	Everolimus	Improved endothelin-induced calcium flux	[282,283] Phase II CTs in AMD
	Homotaurine	Modulates ER stress, Ca^{2+} homeostasis	[284,285] In combination with vitamin E and citicoline increases contrast sensitivity in glaucoma patients
	Isradipine	Blocks L-type Cav channels	[286,287] Did not show efficacy in Phase III CT in PD
	Lutein	Inhibits TRP	[288] Lutein serum levels are associated with decreased AMD progression
	Memantine	Non-competitive blockade of NMDARs	[289–293] Approved for the treatment of AD. Phase II CT in PD. Phase III CTs did not prevent glaucoma progression
	Metformin	Reduces calcium influx	[294,295] Retrospective studies associate metformin with decreased risk of AMD
	Mynocicline	Chelates Ca^{2+} decreases calcium influx	[296–298] Phase II CT in AMD and RP
	Nilvadipine	Blocks L-type Cav channels	[219,299] No benefits observed in Phase III CTs in mild to moderate AD. Phase II CT shows that could retard progression of visual field defect in RP
	Rapamycin	Binds to calcium channels and FKBP52, affects intracellular calcium signaling	[300] Phase II CT in AMD. Well tolerated subconjunctival. No benefits observed in Phase I/II CTs subconjunctival nor intravitreal
	Riluzole	Blocks glutamatergic neurotransmission	[301,302] Phase II CT in MS, delays progression. To see if it also delays retinal damage
	Somatostatin	Blocks L- and T-type Ca^{2+} channels, inhibits calcium influx	[270] Neuroprotective effects in RP patients, after topical administration. Phase II CT
	Talampanel	Non-competitive AMPA antagonist	[303,304] Failed in Phase II CTs in ALS patients
	Ubiquinone, CoQ	Suppresses voltage-dependent calcium influx and MAPK signaling	[305–308] Safe and well tolerated. Administered topically improves RGC loos in AD patients. Good clinical outcomes in phase II CT in DR
	Unoprostone	Inhibits calcium influx. Activates large conductance Ca^{2+}-activated K^+ (BK) channels	[309,310] Well tolerated topically. Increased macular sensitivity in RP patients. Phase II CT for RP
Mitochondrial dysfunction / oxidative stress	9-cis β Carotene	Scavenger	[203,311–313] Well tolerated orally. Poorly absorbed. Phase II CT for RP
	Alpha lipoic acid	Inhibits p38MAPK pathway. ROS scavenger	[314,315] Well absorbed orally. Negative outcomes in GA
	BN82451B	Several mechanisms proposed: socium channel blocking potential (antiexcytotoxic), antioxidant, anti-inflammatory (COX inhibitory potential), and mitochondrial protective	[316] Poorly tolerated. Phase I CT in Huntington disease
	Creatine	Antioxidant. Stabilizes mitochondrial membranes. Also stimulates glutamate uptake into synaptic vesicles	[317,318] Good safety profile and well tolerated. Phase II CT for ALS
	Curcumin	Regulates ROS and mitochondrial depolarization. Decreases oxidative stress	*See above*
	Doxycycline	Scavenges ROS	[319–321] Phase II CT in DR. Well tolerated
	Edaravone	Free radical scavenger	[322,323] Approved by FDA for ALS. Phase II CT for alcohol-induced brain injury. Phase II CT for acute ischemic stroke patients.
	Ethyl eicosapentaenoic acid (EPA)	Free radical scavenger	[324] Phase II CTs for AD. Phase III for AMD (DHA/EPA)
	Finerenone	Decreases oxidative stress, atenuates endothelial dysfunction	[325] Observational study with DR patients
	Hydroxycloroquine	Inhibits calcium channels	[326,327] Preliminary promising results for EM, not for AD
	Metformin	Inhibits Complex I. Redox regulator	[328] Phase I CT for MS. Phase I DR. Phase II CT for AMD
	Lutein	Decreases oxidative stress.	[329] Phase II CT in RP
	MitoQ	Antioxidant that supports mitochondrial function	[330] Phase II CT in MS and PD
	Minocycline	Radical scavenger	[331] Phase II CT in RP and AMD
	N-acetylcysteine	Antioxidant	[332,333] Phase II CT in RP. Safe administered orally, but results are still inclonclusive
	Pioglitazone	PPARγ agonist	[334] Phase III CT in patients with Friedreich's Ataxia
	Pridopidine	Sigma-1 receptor agonist. Enhances mitochondrial function	[335,336] Phase II CT in patients with Huntington's disease. Well tolerated. Still not conclusive data.

(*continued on next page*)

Table 3 (*continued*)

Pathogenic pathway	Small molecule	Mechanism of action	References
	Rapamycin	Decreases oxidative stress	*See above*
	Ruboxistaurine	Inhibits PKCβ and reduces oxidative stress	[337] Tested in CTs for indications related to diabetes, including DR
	Sulodexide	Antioxidant. Preserves endothelial function	[338,339] Prevents cognitive impairment in AD. Tested in DR for the treatment of hard exudates
	Ubiquinone, Coenzyme Q10	Quenching of free radicals	[340,341] Phase II CT in DR suggest therapeutic efficacy. Tested in several brain disorders as AD, PD, MS, epilepsy, depression. Well tolerated, negligible side effects
	Urate	Antioxidant (given as inosine)	[342] Good profile of safety and tolerability. Negative outcomes
	Zeaxanthin	Decreases OS	[343,344] Encouraging results in AMD and glaucoma after dietary supplementation
Neuroinflammation / microgliosis / P2X7 receptors	AZD3241	Inhibitor of myeloperoxidase	[345] Tested in patients with PD and Multiple System Atrophy. Safe and well tolerated
	AZD9056	Blocker of P2X7Rs	[346] CT in patients with rheumatoid arthritis, with negative outcomes but good tolerability.
	Celecoxib	COX inhibitor	[347] Phase III CTs in Tested in AD. Initially no good outcomes
	Curcumin	Decreases P2X7R expression and activation. Represses NLRP3 inflammasome activation via P2X7 activation Amends Ca^{2+} dysregulation in microglia (via P2X7R)	[275] *See above*
	Exenatide	Agonist of glucagon-like peptide 1 (GLP-1)	[348,349] Phase II CTs in PD and AD. Initial positive outcomes. Ongoing phase III CTs in PD
	Glatiramer acetate	Immunomodulator	[350,351] Approved by FDA for MS. Phase III CTs in AMD with no formal report of results
	Ibuprofen	COX inhibitor	[352] Phase IV CTs in patients with AD
	JNJ-55308942	Blocker of P2X7Rs	[176] 2020. Phase I CTs; good safety profile
	JNJ-54175446	Blocker of P2X7Rs	[176] 2020. Phase II CTs; in depression; negative outcome but good safety profile
	Laquinimod	Down-regulates proinflammatory cytokines and up-regulates anti-inflammatory citokines	[353,354] Phase II CTs in MS. Generally, well tolerated. Initial good results
	Metformin	Inhibits P2X7R	*See above*
	Minocycline	Inhibition of ROS production	*See above*
	Naloxone	Inhibits retinal microglial activation	[355] No beneficious initial results in AD as monotherapy
	Naproxen	COX inhibitor	[356] Phase III CTs in Tested in AD. Initially no good outcomes. Initial disappointing outcomes AD
	Pioglitazone	PPARγ agonist	[334] Phase IV CTs in DR. No results officially posted
	Saffron	Saffron reduces ATP-induced retinal cytotoxicity by targeting P2X7 receptors. Anti-apoptotic, anti-inflammatory, antioxidant	[357,358] Results suggest possible therapeutic potential in retinal degenerative pathologies. Phase I CTs for AMD
	Valproic acid	Inhibits histone deacetylase and autophagy	[359] Heterogeneous clinical repots in RP. Not beneficious for all genotypes.

thickness [204]. In contrast, the supplementation for 3 months with the CAT formula in patients suffering from DM1 or DM2 showed an improvement of visual acuity, contrast sensitivity, and foveal thickness [205].

Another interesting approach has been the association of CAT with anti-VEGF therapies. So, in a study on 55 DM2 patients with diabetic macular edema treated with CAT and ranibizumab for 3 years, authors found lower macular thickness in the group supplemented with antioxidants, compared with control patients [206]. An additional effective combination was fasudil (a rho kinase inhibitor) and anti-VEGF bevacizumab; intravitreal injection of both agents improved visual acuity in patients with diabetic macular edema [207].

Various antioxidants (flavonoids, coenzyme Q, N-acetylcysteine, vitamin C, calcium dobesilate) have been studied in CTs, with erratic controversial results (see [112,176]). Two recent CTs with antioxidant saffron-derived compounds (safranal, crocetin, and dimethylcrocetin) show promising early data for the treatment of diabetic maculopathy [208]. A recent CT has shown a synergistic effect of the co-administration of curcumin, homotaurine, and vitamin D3, decreasing soluble mediators of inflammation and retinal damage, so suggesting the potential benefits of a multi-target strategy [209]. A few molecules with effect on cytosolic Ca^{2+} levels have been tested in CTs against AMD. This is the case of α-lipoic acid, empagliflozin, rapamycin, or ubiquinone, all of them with other mechanisms of action [176].

In summary, CTs with single or combined antioxidant drugs in DR patients have provided controversial results. However, some of them are promising, particularly those using combined antioxidants. Long-term studies should consider the efficacy and safety of antioxidants at different doses; this is hard to test with complex formulations containing several compounds. Thus, although there is a tendency to use antioxidants in complex combinations, "cleaner" CTs should be performed with single antioxidants or, at most, with 2–3 combined antioxidants.

5.4. Clinical trials and drug targets in retinitis pigmentosa

An interesting research line focus on advanced therapies in RP; these include gene replacement, genome editing, and stem cells treatments [210–213]. As these treatments might take time in reaching the clinic, focus is being placed in pharmacological approaches to target pathways leading to cell death, in order to delay disease progression [214]. Dietary supplements with antioxidant properties such as vitamin A, docosahexaenoic acid (DHA), and lutein are the prescribed antioxidants in RP. Concerning vitamin A, early CTs reported a protective effect at high doses [215]. In another CT, combined DHA plus vitamin A improved photoreceptor survival [216]. A more recent CT showed a slowing in the progression of visual field loss in patients with X-linked RP, treated with oral daily supplement of DHA for 4 years [217]. Also, a CT in 34 RP patients treated with lutein supplementation for 6 months showed positive clinical outcomes in preserving the central visual field [218].

Long-term treatment with the blocker of L-type Ca^{2+} channels nilvadipine, improved average visual field sensitivity in RP patients. Authors of this study suggested that further improvement could be

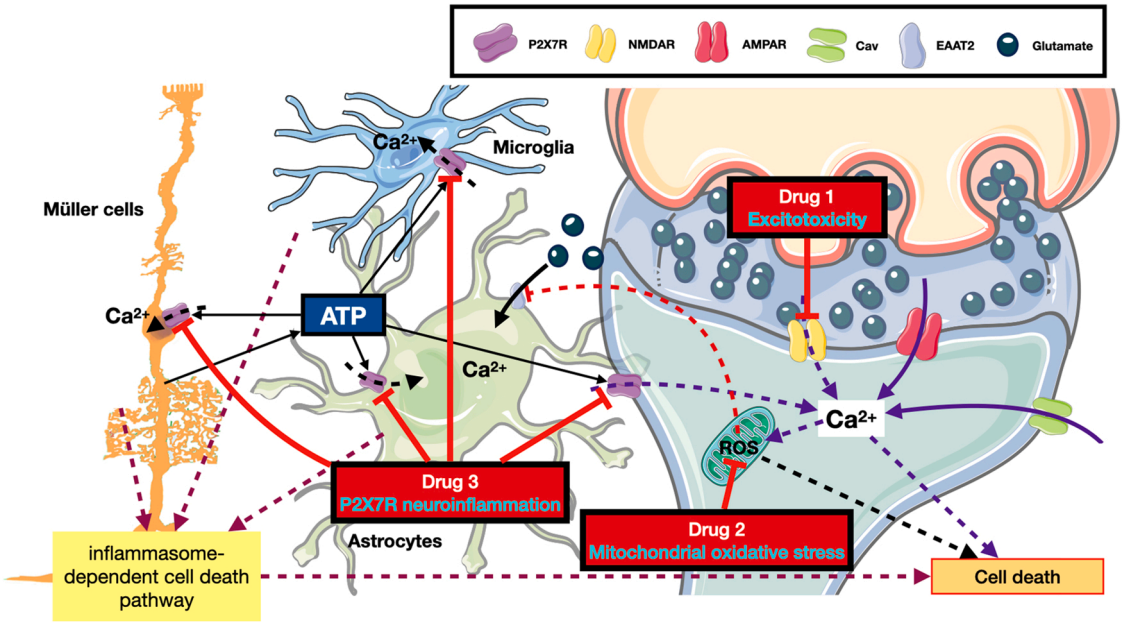

Fig. 9. Scheme showing the proposed combination of three drugs (triads) acting specifically and selectively on each one of the three pathogenic targets that are common to DR, AMD, glaucoma, and RP. F1: drug blocking NMDA channels and reducing Ca^{2+} overload and excitotoxicity; F2: antioxidant drug, reducing oxidative stress; F3: anti-inflammatory drug blocking P2X7Rs. Some images were obtained and modified from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Generic License. http://smart.servier.com/.

Table 4
Proposed triads of repositioned medicines that at low doses may exhibit synergistic retinal protective activity with low toxic effects in retinal degenerative diseases.

Triad	Excitotoxicity	Oxidative stress	Neuroinflammation
Triad 1	Memantine	Pioglitazone	Mynocicline
Triad 2	Nivaldipine	Edaravone	Naloxone
Triad 3	Ceftriaxone	MitoQ	Valproic acid

achieved with the combination of nilvadipine and an antioxidant [219]. Several molecules with effects on cytosolic Ca^{2+} levels have been explored, as cannabidiol (as a plant extract) and also minocycline and ubiquinone, both of them with antioxidant properties too [176].

In summary, targeting oxidative stress with antioxidant supplementation has been the main focus in CTs for RP. Calcium dyshomeostasis has been explored in at least one study with a blocker of L-type Cav channels. Finally, in neuroinflammation some studies focused on chemokine receptor inhibitors; however, no CTs have yet been done with P2X7R blockers to mitigate the neuroinflammatory pathogenic pathway of RP.

6. Multi-target therapy approach to combat chronic diseases

Here, we will discuss the first basis for therapeutic combinations of drugs acting on different but complementary pathogenic signaling pathways in various chronic diseases. We will then extrapolate these concepts to the treatment of retinal degeneration with such drug combinations.

6.1. The "one-target-one-drug" paradigm versus the "multitarget-drug combination" paradigm

The biological definition of a key target in the pathogenic cascade of a given disease led medicinal chemists to strategically design a molecule that interacts with such target with certain degree of selectivity; in doing so, such molecule could become a potential therapeutic candidate for clinical trials, and eventually it may reach the status of a new medicine to treat such disease. Unquestionably, this "one target-one compound" paradigm has been highly successful in the past; for example, in beta-blockers for coronary artery disease, cyclosporine as immunosuppressant in organ transplantation, or proton pump inhibitors in acid gastroduodenal diseases. During the second half of the XX century, hundreds of successful drug therapies have been introduced in the clinic following this research paradigm. More recently, genomic and proteomic studies have revealed new potential targets that gave rise to highly selective medicines essentially based on monoclonal antibodies for inflammatory and cancer diseases. Precisely, these and many other chronic diseases such as cancer [220], hypertension [221], asthma [222] and AIDS [223] are better controlled with combinations of drugs with different but complementary mechanisms of action associated to various targets of the disease.

This multi-target approach is grounded on various facts. One of them is that most cells have a sort of "back-up" systems leading to the same final outcome, namely, gene expression, receptor-triggered signaling pathways, protein synthesis, or protein degradation. Thus, proteins and intermediates involved in these back-up mechanisms may be completely different; hence, drugs targeting a given primary signaling pathway may have no effect over the back-up pathways, a phenomenon known as redundancy [224]. Additionally, cellular networks and signaling pathways are strongly buffered, thus preventing major output changes, in spite of the pronounced changes that their components may undergo [225,226].

So, a multi-target therapy approach can be more efficacious as it may mitigate the redundancy escape by interfering simultaneously with three target pathways; in so doing, this triad of medicines could sequentially act on the complex multiple pathogenic mechanisms giving rise to neuronal death in neurodegeneration [227,228]. Here we propose a novel therapeutic strategy to combat retina degeneration by acting on three common and interrelated pathogenic pathways, namely: (i) excitotoxicity linked to overactivation of NMDARs, AMPARs, and Cav channels with ensuing neuronal and mitochondrial Ca^{2+} overload; (ii) mitochondrial dysfunction and oxidative stress with augmented ROS production and decreased ATP production; and (iii) neuroinflammation linked to P2X7Rs. In the search of three compound candidates in order to

Table 5
Pharmacokinetic characteristics of the repositioned medicines included in Table 4.

Drug	Oral bioavailability (%)	% Bound in plasma	V distribution (L/Kg)	$t_{1/2}$	CYP450 effects	BBB	RBB	Comments
Memantine	100 [371]	45 [372]	9–11 [372]	60–80 h [372]	Low CYP inhibitory promiscuity [373]	+[373]	+ rats [374] + rats and monkeys, experimental glaucoma [375]	Linear pharmacokinetics over the therapeutic dose range. Combination with other drugs as citicoline have shown better pharmacokinetic parameters [376]
Pioglitazone	83 [377] 97 [378]	> 99 [379]	0.63 + / − 0.41 [379] 0.25 [378]	3–7 h, (16–24 h active metabolites) [379] 9 h [377,378]	Inhibitor CYP450 1A2, 2C9, 2C19. High inhibitory promiscuity [379] No effects [377]	+[379, 380]	+ rats, *diabetes model, STZ induced* [381]	20% metabolized by CYP3A4 (possible interindividual variability in PK, possible inhibition by other drugs) [378]
Minocycline	95–100 [382]	76 [383,384]	67.5–115 [383,385]	11.1–22.1 [383]	Low CYP inhibitory promiscuity [383]	+[386]	+ murine ischemia-reperfusion, retinal detachment [387–389]	Needs monitoring for > 6 months treatments (hepatotoxicity, lupus eritematosus, pigmentation) [390]
Nilvadipine	14–19 [391]	97.5–98.7 [392]	94.7 [393]	15–20 [394] 11 + /− 2.3 h [393] 9.8–18.2 [395]	Inhibitor: CYP4501A2, 2C9, 2C19,3A4 High CYP inhibitory promiscuity [396]	−[396]	+ rat retinal ischemia [397]	High first-pass metabolism [394] Substrate of CYP3A4 [396] Therapeutic plasma levels are reached after oral administration [395]
Edaravone	60% [398]	92% [399]	18.5 [400]	4.5–10.9 h [398,400]	No [401]	+[400, 402]	+ mouse model normal tension glaucoma [403]	Well tolerated [404] Protects retina against several insults (isquemia/reperfusion, steptozocin induced diabetes, retinal detachment).
Naloxone	< 2% [405] but significant sublingual absorption [406]	45% [407] 50% [408]	200 [407]	1–2 h [408]	Low CYP inhibitory promiscuity [407]	+[407, 409]	+ mouse [409]	Substrate CYP450 2D6, 3A4 [407] High presystemic metabolism [408]
Ceftriaxone	8% (24% rectal absorption with enhancer) [410]	95% [411]	5.78–3.5 (iv, im) [411] 8.5–10 [412]	5.8–13.5 h (im) [413] 6 h (iv) [412]	Inhibitor CYP450 3A4. High CYP inhibitory promiscuity [413]	−[413] +(low) [414]	Detectable in vitreous after intramuscular administration [415, 416]	Substrate of CYP450 3A4 [413]
Mitoquinone	10% as methane-sulfonate [417, 418]	Binds to serum albumine in vitro [419]		14 h rats [420]	Few information available [421] CoQ10 undergoes structural changes when exposed to CYPs [422]	+[423]	+ mouse inherited photoreceptor degeneration [424]	Accumulates several hundredfolds into the mitochondria. Ongoing several CTs for usefulness in MS, PD, AD, Asthma, and others
Valproic acid	90–100 [425]	82–90 [426]	0.1–0.4 [427]	13–19 h [426] 6–8 h [427] 9–16 h [428]	Low CYP inhibitory promiscuity [426]	+[426]	+ in vitro assays [429,430]	It is absorbed rapidly. Its bioavailability is complete independently of the preparation used [427]

block simultaneously those common pathogenic pathways, we also propose the search of three medicines in clinical use through the shorter strategy of drug repositioning, that we comment next.

6.2. Drug repositioning

For years, the finding of second indications for medicines in clinical use has been fortuitous. For instance, in 1951 isoniazid and its isopropyl derivative iproniazid were developed for the treatment of tuberculosis. When their clinical use started, it was soon found that iproniazid (but not isoniazid) had mood-elevating effects in tuberculosis patients; this was associated to its ability to block the enzyme monoamine oxidase (MAO), that allowed the introduction of MAO inhibitors in psychiatry for the treatment of depressed patients [229]. A few other serendipitous discoveries of second indications of drugs opened the way for a more systematic search of new indications for old drugs, so called repositioning or repurposing approach, that started to gain interest at the beginning of this century [230].

The principle that establishes the basis of drug repositioning can be defined as multiple compound-targets; this refers to the phenomenon by which the majority of compounds and medicines bind to more than one biological target; in so doing, they exhibit pharmaco-physiological effects secondary to the initially desired one [231]. In addition, one single target can be relevant in more than one mechanism of disease. Two main tools are being followed in repositioning programs: (i) generation of connection hypotheses through literature-based search of related

cellular and pathogenic mechanisms; (ii) study of bioinformatic features, pharmacological properties and prediction of interactions via computational approaches [232]. These two complementary approaches offer valuable insights into the relationships between drugs, targets and diseases, which are key for successful repositioning. The increasing attention to this strategy during the last two decades is grounded on the following facts: (i) increasing high costs of drug discovery and development [233]; (ii) lower number of drugs approved by regulatory agencies each year [234]; (iii) several steps of the drug development pipeline can be skipped during drug repositioning; (iv) the candidate drug has a known biological effect in humans and comply with the requirements of safety and bioactivity. Thus, in most cases the evaluation of a suitability of a repositioned drug is directly initiated in phase II studies. This shortens the time span of development, reduces risks, and compensates for the economic pressure characteristic of pharma industry [235].

There is a long list of examples of repositioned drugs; Table 2 shows some critical and interesting examples. Overall, approximately 170 drugs entered the process of repositioning approach; the majority of them are in distinct phases of clinical trials and around 10% of them have been approved, which denotes an advantageous outcome in comparison to the standard drug development program.

6.3. The pharmacological basis of drug combinations

As discussed above, the repositioning of approved medicines has gained new momentum for the rapid identification and clinical development of new therapeutic indications for diseases that lack effective treatments. This strategy has proven to be successful in the last decade. Nevertheless, a limitation of this approach has been the relatively low potency that some of the repositioned medicines exhibit on the new explored target. Thus, upon their oral administration, they may produce tolerated plasma concentrations that may be lower than those required for therapeutic efficacy. This unfavorable therapeutic/safety ratio may be overcome by the combination of two or more medicines with different but complementary mechanisms of action in disease pathogenesis; this combination is an alternative approach to increase the success rate of drug repositioning [256–258].

By targeting different pathogenic signaling pathways, the use of drugs in combinations may provide a synergistic therapeutic effect. This results in a reduction of the required effective drug concentration for each individual drug, with respect the concentration required to inhibit its specific target. Once identified in a given repositioning program, the selected drugs can be tested on in vitro and in vivo models of the disease being explored. For instance, a study found that at sub-threshold concentrations with no effect for single drugs, the association of melatonin and galantamine afforded a synergistic neuroprotection in neuronal cultures [259] (Fig. 8A). Also, in an in vivo model of stroke in mice, additive effects in reducing infarct volume with combined citicoline and nimodipine were found [260]. So, drug combinations may allow administration schedules at doses low enough to achieve the desired therapeutic effect at human plasma concentrations below their toxicity effects [261] (Fig. 8B). This has been particularly successful in cancer, were combined drugs exhibit superior efficacy and safety, compared with monotherapies [262].

Drug-drug interactions may also limit the combination of medicines. Although pharmacodynamic interactions may occur, pharmacokinetic (PK) interactions are the most common. Such is the case of the estrogen receptor modulator tamoxifen and the selective serotonin reuptake inhibitor paroxetine that is used to treat breast cancer in women with depression. Cytochrome P450 2D6 (CYP2D6) metabolizes tamoxifen to its active metabolite endoxifen; thus, in inhibiting CYP2D6, paroxetine decreases the metabolism of tamoxifen, thereby diminishing the endoxifen levels [263]. A latter study demonstrated enhanced risk of death from breast cancer in women who took paroxetine and tamoxifen, compared with women taking only tamoxifen [264]. Thus, care must be exerted in drug combinations, that should be avoided when one of them inhibits CYP3A4, as it is the case for ketoconazole, that leads to higher toxic levels of the other drugs [265]; or contrarily, the drug may induce CYP3A4, such as rifampicin, leading to lower plasma levels and lower efficacy of the other drugs [266].

In summary, there are three major advantages for combination therapies emerging from drug repositioning strategies: (i) the potential for synergistic effects that significantly reduces drug concentrations for each of the individual drug; this greatly augments the chances of their application in combination, which are otherwise insufficiently active as single agents; (ii) the reduction or delay of the development of drug resistance as a result of multiple targeting mechanisms of the drug combinations; and (iii) the partial inhibition of a small number of targets could be more therapeutically efficient than complete inhibition of a single target [267].

7. Combined drug triads for synergic neuroprotection in retinal degeneration

Clinical trials with drug combinations in neurodegenerative diseases are scarce. For instance, in AD, only 2% of phase II CTs and 6% of phase III CTs were done with drug combinations [268]. This is also true for eye diseases leading to retinal degeneration; here, drug combinations have been practically restricted to antioxidant compounds [3,269]. Table 3 collects the drugs (small molecules) and mechanisms of action on Ca^{2+} dyshomeostasis/excitotoxicity, oxidative stress/mitochondrial dysfunction and neuroinflammation/P2X7Rs, addressed in CTs.

Multitarget single drugs or drug combinations addressed to different targets are the two approaches that look for a higher efficacy to combat retinal degeneration with lower side effects. Some examples illustrate the first approach. Thus, in DR, curcumin has shown to alter Ca^{2+} mobilization, (i) by modulating or blocking L-type Cav channels [360,361], (ii) by decreasing oxidative stress through regulation of ROS and mitochondrial depolarization [362–364] and through diminution of the expression and activation of P2X7Rs [365], and (iii) by amending Ca^{2+} dysregulation in microglia [366]. So, this is an illustrative example of a multi-target single molecule. Another example is the antidiabetic metformin [367], that has been explored in DR and AMD, showing decreased oxidative stress and inflammation by modulating P2X7R-mediated signaling pathway [368] and by decreasing Ca^{2+} influx as well [367]. Of interest is also the reduction by saffron of ATP-induced retinal cytotoxicity, by altering the P2X7R-mediated Ca^{2+} signaling in a model of DR [369]. Finally, in glaucoma taurine has been shown to modulate ER stress and Ca^{2+} homeostasis thereby protecting against P2X7R-mediated toxicity [370].

The second approach is related to the combination of three drugs (triads) acting specifically and selectively on each one of the three pathogenic targets that are common to the four eye diseases here discussed, namely, DR, AMD, glaucoma, and RP (Fig. 9). The proposal implies the systemic oral administration of the triad as to complement and reinforce the topical eye treatments currently used. As the triads are intended to be selected in the frame of a program of repositioned drugs in clinical use, their pharmacodynamic and pharmacokinetic properties are well known. The ideal properties of the triad medicines should therefore comprise: (i) known effective drug concentrations for their main activity (ED_{50}); (ii) lipophilicity to cross cell membranes and so, to pass through the brain-blood barrier (BBB) and retinal-blood barrier (RBB); (iii) low first-pass hepatic extraction and poor metabolism by cytochrome P450 liver enzymes; (iv) lack of P450 enzyme induction or inhibition to prevent drug-drug interactions; (v) ample toxicity window with a large therapeutic ratio.

Looking at the drugs included in Table 3, that have been or are being tested in CTs, the following triads are proposed (Table 4). The PK characteristics of these 9 medicines are summarized in Table 5. These three triads are being suggested as examples of drugs that have optimal characteristics to cross the BBB, do not have high interactions with the

hepatic cytochrome P450 and a good bioavailability.

8. Conclusions and perspectives

Blindness due to retinal degeneration is a major health problem. Poor quality of life for patients and their families and a huge burden to society and health systems are some of these health, social and economic problems. Here we focused on four eye diseases that are major causes of retinal degeneration namely, glaucoma, AMD, DR, and RP. Until gene- and cell-based therapies evolve to successfully target the etiology and/or restore the cell functionality in neurodegenerative diseases, a pharmacological approach is, for now, our best chance to slow down the degenerative process. These diseases have multiple etiologies which are unknown in most cases. From a pathogenic point of view, they have myriad mechanisms and signaling pathways that are specific for each one. However, they also share some mechanisms that end up with degeneration of the different retinal cell types, ie, Ca^{2+} overload (NMDAR and AMPAR mediated excitotoxicity), oxidative stress (distorted mitochondrial Ca^{2+} handling with augmented free radical production by the respiratory chain), and neuroinflammation (overactivation of the inflammasome by P2X7R overstimulation by high ATP concentrations locally released by damaged tissues). Here we argue that redundancy of several pathogenic pathways can compensate one of them that has been blocked by a single drug. This could explain the failure of hundreds CTs with a single-test compound, that provided negative outcomes in both brain neurodegenerative diseases and the pathogenically related eye diseases leading to retinal degeneration. CTs with combined drugs have provided highly positive outcomes in several chronic diseases as cancer, AIDS, cardiac failure, asthma, the epilepsies, Parkinson's disease, or major depression. In spite of this vast evidence in favor of drugs combinations, scarce if any clinical trials are being done with drug combinations in both brain neurodegenerative diseases and retinal degeneration.

In this review, we provide strong arguments to ground the hypothesis that a triad of repositioned medicines could generate better outcomes in CTs with patients suffering from retinal degeneration. These three medicines showing complementary mechanisms of action on excitotoxicity, oxidative stress, and neuroinflammation may lead to better outcomes in clinical trials in patients suffering from glaucoma, AMD, DR, and RP. A major challenge to this strategy could be the potential PK interactions between the three medicines included in a given therapeutic triad. However, as the PK profiles of these medicines in medical use are well known, those interactions may be overcome.

In the middle of a high scientific controversy, the FDA just approved the anti-amyloid beta (anti-Aβ) monoclonal antibody aducanumab; the outcomes from two large phase III clinical trials were modest in one trial and negative in the other. The cost of such medication will be around 40.000 euros/year, with monthly administration of the antibody for an undetermined time. Nevertheless, the FDA has asked Biogen, the company that will manufacture the medicine, to perform a novel phase III clinical trial. This example illustrates, once more, the problem of addressing a treatment to combat the complexity of neurodegeneration processes with a single-target drug. For reasons of patent protection and competitive business, pharmaceutical companies rarely agree in performing a clinical trial with combinations of their proprietary drugs. This reluctancy may be overcome by academia, with programs of drug repositioning that have been quite successful in the last decades. We predict that a combined triad of old medicines that went out of patent protection, targeting the three pathogenic mechanisms here addressed, will provide better outcomes in clinical trials aimed at testing its potential to prevent and delay retinal degeneration and blindness in patients suffering from glaucoma, AMD, DR, and RP; this may be even more successful if triads are added as adjunct to standard current treatments of glaucoma, AMD, DR, and RP. To date, many scientific and economic efforts, have been made to slow or stop retinal degenerative processes. Here we propose a new approach that considers more than one target. The whole way to the elucidation of the therapeutic possibilities and applicability of these triads is long but, considering the efforts made up to date and the results obtained so far, we consider it worth to try.

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CRediT authorship contribution statement

AGG conceived the manuscript. **AGG and VM** drafted the manuscript. **VM and AMG** searched for bibliography. **AGG, VM, PL, NC and AMG** designed the figures. **AGG and VM** designed the tables. **AGG, VM, AMG, PL and NC** revised the final manuscript.

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