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Revisiting the renin-angiotensin-aldosterone system in the eye: Mechanistic insights and pharmacological targets

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ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) plays a fundamental role in regulating blood pressure and fluid homeostasis through key effectors such as angiotensin II and aldosterone. These agents and their receptors have become crucial molecular targets in several cardiovascular and renal diseases. Over the past few decades, a growing body of evidence has revealed the presence of RAAS components in ocular structures, suggesting a tissue-specific RAAS within the eye. Building on this knowledge, studies have indicated that the ocular RAAS plays a significant role in the pathogenesis of various eye diseases. An impaired and overactivated RAAS contributes to the development of severe and widespread disorders affecting both the anterior and posterior segments of the eye. In this context, the current work aims to delve into the pivotal molecular pathways involving the RAAS, with an in-depth exploration of the ocular pathophysiology. It focuses on the relationship between overactivation of the RAAS and oxidative stress, as well as the exacerbation of neovascularization and inflammatory processes. The objective is to provide an updated and comprehensive understanding of the role of the RAAS in ophthalmological diseases, highlighting the therapeutic potential of RAAS modulators and discussing the controversies and challenges in this area of research.

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) is one of the most intensively studied hormonal networks, serving as a significant physiological regulator of blood pressure and body fluid homeostasis. Chronic activation of the RAAS leads to several pathogenic effects, including arterial hypertension, inflammation, endothelial dysfunction, neovascularization, and oxidative stress [1–7]. Therefore, it is not surprising that RAAS blockade offers therapeutic benefits, effectively addressing pathophysiological conditions such as elevated blood pressure and hyperglycemia, making it essential for managing cardiovascular and renal disorders [8].

The pathogenic relevance of the RAAS has also been described beyond the cardiovascular system and kidneys [9–11].

Specifically, most RAAS components have been identified in ocular structures such as the retina, ciliary body, and choroid [12,13]. This discovery has sparked increasing ophthalmologic interest over the past few decades, positioning the RAAS as a potential therapeutic target due to its regulatory role in eye physiology [14]. Current research has explored the role of the RAAS in the pathophysiology of common and debilitating ocular disorders such as glaucoma, cataract, diabetic retinopathy (DR), age-related macular degeneration (AMD), retinal vein occlusion (RVO), retinopathy of prematurity (ROP), central serous chorioretinopathy (CSCR), epiretinal membrane (ERM), and uveitis. This research highlights the potential for novel treatment strategies targeting RAAS components to manage these ophthalmological diseases [15–28].

Against this backdrop, this review article aims to summarize advances in the understanding of the ocular RAAS, particularly focusing on the involved signaling pathways and their connection to inflammation and oxidative stress in ocular diseases. Furthermore, we will present and discuss the related therapeutic implications.

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2. The RAAS in the eye and related signaling pathways

2.1. The RAAS: general mechanistic insights

The classical RAAS is a crucial endocrine system regulating blood pressure (BP), fluid volume, and electrolyte balance, which is heavily involved in inflammation and neovascularization [29]. Mechanistically, the RAAS begins with the production of preprorenin by juxtaglomerular cells in the kidney, which is then cleaved to prorenin and released as prorenin or renin [30,31]. Renin, an aspartyl protease and the rate-limiting enzyme of the RAAS, catalyzes the conversion of angiotensinogen to angiotensin I (Ang I), which is subsequently converted by angiotensin-converting enzyme (ACE) into angiotensin II (Ang II) [32,33]. Ang II, a central player in the RAAS, interacts with two main receptors, the angiotensin type 1 receptor (AT1R) and the angiotensin type 2 receptor (AT2R) [34]. Binding of Ang II to the AT1R triggers vasoconstriction, inflammation, and neovascularization [35–37]. Ang II also stimulates aldosterone production from the adrenal glands, which plays a key role in fluid homeostasis and further contributes to inflammation and neovascularization through its interaction with the mineralocorticoid receptor [38].

However, the RAAS also features a protective counter-regulatory axis via the AT2R and the Mas receptor (MasR) [39]. In fact, binding of Ang II to the AT2R induces vasodilation and exerts anti-fibrotic and anti-inflammatory effects [40]. ACE2, an ACE homologue, converts Ang I to Ang (1−9) and Ang II to Ang (1−7), with the latter binding to the AT2R and the MasR to counteract the effects of the AT1R [41–48].

Recent studies have also highlighted a novel RAAS pathway involving the (pro)renin receptor [(P)RR], which binds both renin and prorenin independently of Ang II, triggering inflammation and tumorigenesis [49–54].

2.2. Expression of RAAS components in the eye

A local, tissue-specific RAAS has been identified in various human organs, including the eye [14]. Components such as Ang II, ACE, the AT1R, and the MasR have been found in ocular tissues like the retina and ciliary body, suggesting the potential for targeting these enzymes or receptors in treating ocular disorders [12,13,55–61]. Although the existence of an ocular RAAS independent of the circulating system was initially debated and remains somewhat controversial, evidence supports this concept [8,55,62]. The blood-retina barrier typically prevents circulating RAAS components from entering ocular tissues. However, significant concentrations of pivotal RAAS agents, such as Ang II, have been found in ocular structures, indicating local synthesis and expression of an ocular RAAS [8,14]. This hypothesis is further supported by mRNA expression studies showing the presence of RAAS components like renin and ACE in ocular tissues [57,63]. Additionally, components of the RAAS counter-regulatory arm have been detected in the eye, potentially playing a role in conditions such as diabetic retinopathy and glaucoma [64,65].

2.3. Cellular signaling cascades of the ocular RAAS

2.3.1. Angiotensin signaling in the eye

Ang II synthesis in the eye is primarily localized in retinal glia, as suggested by the presence of angiotensinogen mRNA in rat retinal glial cells [66]. Human Müller cells, key retinal glial cells, also produce and process Ang II and its metabolite Ang (1–7), indicating the importance of local Ang II signaling for neurovascular autoregulation [67]. In fact, from a physiological point of view, Ang II may be central in retinal blood vessel constriction, regulation of glial cell and neural function [68,69]. Specifically, dedicated investigations have assessed that Ang II is able to trigger constriction of pericytes, retinal endothelial cell apoptosis, collectively leading to reduction of retinal arteriole diameter and blood flow [70–72].

Mechanistically, Ang II binding to the AT1R activates intracellular cascades via phospholipase C (PLC), leading to the inositol-1,4,5-triphosphate (IP3)/Ca^{2+} axis and the diacylglycerol/protein kinase C (DAG/PKC) pathway [12,73–75]. These cascades promote inflammatory and angiogenic responses by synthesizing mediators such as TGF-β1, VEGF, ICAM-1, MMPs, and NOX, causing inflammation, oxidative stress, and fibrosis [76–81]. With regard to the Ang II-related oxidative stress, we recently demonstrated that Ang II triggers endothelial dysfunction in murine ophthalmic arteries through activation of the AT1R and NOX2-dependent superoxide anion radical ($O_2^{\bullet-}$) formation, suggesting that blockade of the AT1R and NOX2 pathway may be helpful to restore endothelial function in the ocular microvasculature impaired by ocular diseases [7]. Along with NOX2, Ang II stimulates the generation of $O_2^{\bullet-}$ by NOX1 and NOX5 via the AT1R, while it triggers the synthesis of hydrogen peroxide (H_2O_2) directly via NOX4 and indirectly through the superoxide dismutase (SOD)-related conversion of $O_2^{\bullet-}$ produced by NOX1, NOX2, and NOX5 [82–84]. In ophthalmological research, studies on the effects of the ocular RAAS in glaucoma, cataract, DR, AMD, ROP, and CSCR have confirmed that along with NOX2, NOX1 and NOX4 are also involved in the oxidative damage linked to the activation of the AT1R by Ang II, while no studies have suggested a role for NOX3, NOX5, DUOX1, and DUOX2 [85–95].

Conversely, AT2R signaling, triggered by Ang II or Ang (1–7), induces vasodilation and exerts anti-fibrotic, anti-inflammatory, and antioxidant effects, possibly via the phospholipase A2/cyclic guanylate monophosphate/nitric oxide axis [14,96,97]. This pathway suppresses Ang II-related NF-kB activation and ROS formation, although AT2R also modulates angiogenesis via VEGF release [98,99].

The Mas receptor (MasR), another G protein-coupled receptor in the eye, binds Ang (1–7) and produces anti-inflammatory and anti-fibrotic effects [100,101]. While specific ocular studies on MasR are limited, it generally attenuates ERK1/2 axis activation induced by Ang (1–7) binding to AT1R, modulating Gαi-adenylyl cyclase and decreasing NF-kB activation [102,103]. The MasR also suppresses the SMAD2 pathway, reducing TGF-β1 expression and fibrogenesis [104]. Additionally, the MasR has been shown to mediate anti-proliferative and anti-tumorigenic effects by downregulating the PI3K/Akt/mTOR signaling pathway [105].

Ang II also contributes to generation of ROS, through its action on the mitochondria, as studies on skeletal muscle, vascular tissue, heart and kidney have determined [106–113]. In fact, the Ang II-induced activation of NOX2 and the subsequent ROS formation have been reported to trigger the opening of the mitochondrial ATP-sensitive potassium channel (mtKATP) in the mitochondrial membrane, thereby inducing the aperture of permeability transition pores (mPTP), collectively leading to an escalation of the Ang II-related oxidative stress [114–118]. Moreover, Mitsuishi and colleagues have determined in myocytes that Ang II can induce a decreased mitochondrial biogenesis via a down-regulation of an essential factor like the peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) in an AT2R dependent manner, while can trigger augmented mitochondrial degradation through mitophagy, via ROS-induced AT1R activation [106]. Conversely, another investigation on skeletal muscle conducted by Silva and associates has demonstrated that Ang II was responsible of a reduction in autophagosome formation possibly via an inhibition of the adenosine monophosphate-activated protein kinase (AMPK) and activation of the mammalian target of rapamycin complex 1 (mTORC1) signaling, resulting in suppression of the Unc51-like autophagy activating kinase 1 (ULK1), a serine-threonine kinase involved in autophagy during stress [112]. In another study by Li et al. on osteoblasts, Ang II was able to trigger mitochondrial oxidative stress by suppressing the axis sirtuin 1 (SIRT1)-Forkhead-Box-Protein O3A (Fox03A)-SOD [119]. Of note, the existing literature lacks specific investigations testing the effects of the ocular RAAS in mitochondria.

2.3.2. Microvascular dysfunction and angiotensin II

Importantly, Ang II triggers an overabundance of $O_2^{\bullet-}$ through the hyperactivation of NOX1/2. Under these conditions, an inactivation of the endothelial nitric oxide synthase (eNOS) cofactor tetrahydrobiopterin occurs, which induces the uncoupling of eNOS. This uncoupling indirectly causes the eNOS-mediated production of the powerful reactive nitrogen species peroxynitrite ($ONOO^-$) [120]. Moreover, H_2O_2 blocks dihydrofolate reductase, an enzyme that catalyzes the conversion of dihydrobiopterin to tetrahydrobiopterin, further decreasing tetrahydrobiopterin bioavailability and aggravating eNOS uncoupling [82,121–123]. Regarding the impact of Ang II on eNOS functionality, an interesting *in vitro* investigation conducted by Kondapalli et al. on human microvascular endothelial cells found that Ang II infusion induced, in an AT1R-dependent manner, a downregulation of the Transient Receptor Potential Vanilloid 4 (TRPV4) channels. This downregulation reduced TRPV4-related eNOS phosphorylation and NO production [124]. Hence, the authors suggested that Ang II triggers endothelial dysfunction and vascular remodeling via blockade of TRPV4/eNOS pathway.

Fig. 1 illustrates the molecular mechanisms responsible of the Ang II-induced oxidative stress, through the effect on NOX, mitochondria, and eNOS.

2.3.3. Prorenin signaling in the eye

In the eye, the (pro)renin receptor ((P)RR) interacts with prorenin to activate both RAAS upstream cascades and specific RAAS-independent pathways. This interaction phosphorylates extracellular signal-regulated kinase (ERK) 1/2, modulating the expression of pathogenic agents such as monocyte chemotactic protein (MCP)-1 and intercellular adhesion molecule (ICAM)-1 [125,126]. The RAAS-independent pathway, known as the receptor-associated prorenin system (RAPS), also activates the expression of TGF-β1 and extracellular matrix proteins like type I collagen and fibronectin in hypertensive animal models, leading to fibrosis [127–130].

Studies have highlighted the significant role of (P)RR in ocular inflammation, fibrosis, and retinal neovascularization, particularly in diseases such as AMD and uveitis [131–138]. Of note, (P)RR also contributes to fibrosis in proliferative diabetic retinopathy (DR) and idiopathic epiretinal membrane [139,140]. Since direct renin inhibitors and other RAAS modulators do not act upstream of the (P)RR, these do not affect the RAAS-independent pathways [141]. This underscores the potential for designing specific molecules to directly suppress (P)RR in ocular disorders.

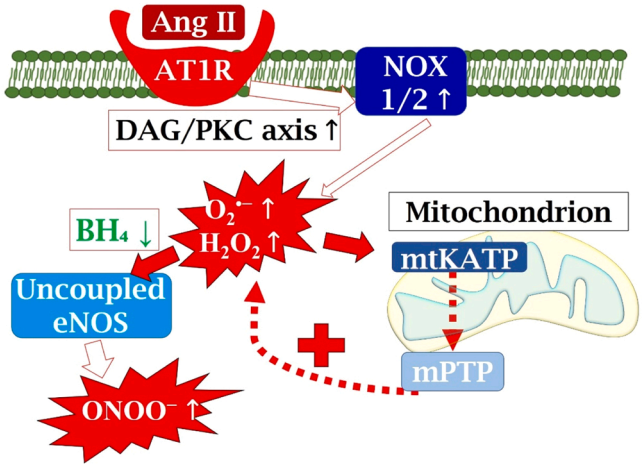

Fig. 1. Schematic representation of the main intracellular cascades activated by Ang II and the AT1R, leading to oxidative stress. Ang: angiotensin; AT1R: angiotensin II type 1 receptors; BH_4: tetrahydrobiopterin; DAG/PKC: diacylglycerol/protein kinase-C; eNOS: endothelial nitric oxide synthase; H_2O_2: hydrogen peroxide; mPTP: mitochondrial permeability transition pore; mtKATP: mitochondrial ATP-sensitive potassium channel; NOX: nicotinamide adenine dinucleotide phosphate oxidase; $O_2^{\bullet-}$: superoxide anion radical; $ONOO^-$: peroxynitrite.

2.3.4. Aldosterone signaling in the eye

Aldosterone binds to the mineralocorticoid receptor, a classical steroid hormone receptor in the nuclear receptor subfamily 3. Upon binding, the mineralocorticoid receptor-ligand complex migrates to the cell nucleus to induce the expression of genes crucial for fluid homeostasis [142,143]. Preclinical investigations have shown that aldosterone triggers retinal edema by upregulating ion channels such as the epithelial sodium channel ENAC-α, the inward rectifying potassium channel Kir4.1, and the water channel AQP4 in retinal Müller cells [144]. Another study found that aldosterone causes choroidal thickening, vasodilation, and leakage, potentially via the small conductance calcium-activated potassium channel 3 (KCa2.3) in choroidal endothelial cells [145]. Recent research has demonstrated that endothelial deletion of the mineralocorticoid receptor reduces the severity of choroidal neovascularization (CNV), highlighting the role of aldosterone in retinal vascular dysfunction [146]. Of note, aldosterone is also a key driver of inflammation and neovascularization in various ocular disorders [147]. Furthermore, it promotes oxidative stress by enhancing the transcription and plasma membrane translocation of pro-oxidative agents, such as the NADPH oxidase complex (including NOX2 and NOX4) in endothelial cells, leading to an overabundance of reactive oxygen species (ROS) [148,149]. Interestingly, aldosterone has also been reported to induce a downregulation of its receptor during ocular inflammatory disorders, such as uveitis, suggesting a negative feedback loop that may have anti-inflammatory effects [150].

Fig. 2 provides a schematic overview of the primary molecular intracellular transduction pathways activated by angiotensin, prorenin, and aldosterone, highlighting the key pathogenic downstream effects of these cascades.

2.4. The kallikrein/kinin system

2.4.1. General aspects of the kallikrein/kinin system

The kallikrein-kinin system (KKS) is a multi-enzymatic and peptidergic system, essential in human physiology, in nociception, and in inflammation [151–153]. Central players of the KKS are the plasma and the tissue kallikreins, which are able to generate powerful vasoactive peptides, named kinins, specifically bradykinin (BK) and kallidin (KD), from specific substrates called kininogens [153]. Subsequently, a kininase I like for example the carboxypeptidases N, can generate des-Arg^9-BK, and des-Arg^{10}-KD, from BK and KD respectively. Alternatively, kininase II, better known as ACE, transforms BK and KD as well as des-Arg^9-BK and des-Arg^{10}-KD into inactive fragments [152,154,155].

Main targets of the kinin signaling are the bradykinin type 1 and type 2 receptors (B1R and B2R), two G-protein-coupled receptors. BK and KD are the endogenous activators of B2R, whereas their kininase I-generated inactive fragments, des-Arg^9-BK and des-Arg^{10}-KD, are agonists of B1R [156,157].

B1Rs are typically expressed at low physiological levels but become upregulated in response to inflammation or injury. Notably, the B1R activates NOX and iNOS, thereby contributing to vascular inflammation and endothelial dysfunction [158–160].

In contrast, activation of the B2R promotes vascular permeability and vasodilation by increasing intracellular calcium in smooth muscle and endothelial cells. This initiates downstream signaling pathways such as eNOS and phospholipase A2, ultimately leading to the generation of nitric oxide (NO), prostacyclin, and tissue plasminogen activator (t-PA) by endothelial cells [153]. Interestingly, the B2R has also been associated with anti-inflammatory effects, particularly in the heart and brain, where its activation may counteract inflammatory responses [161–163].

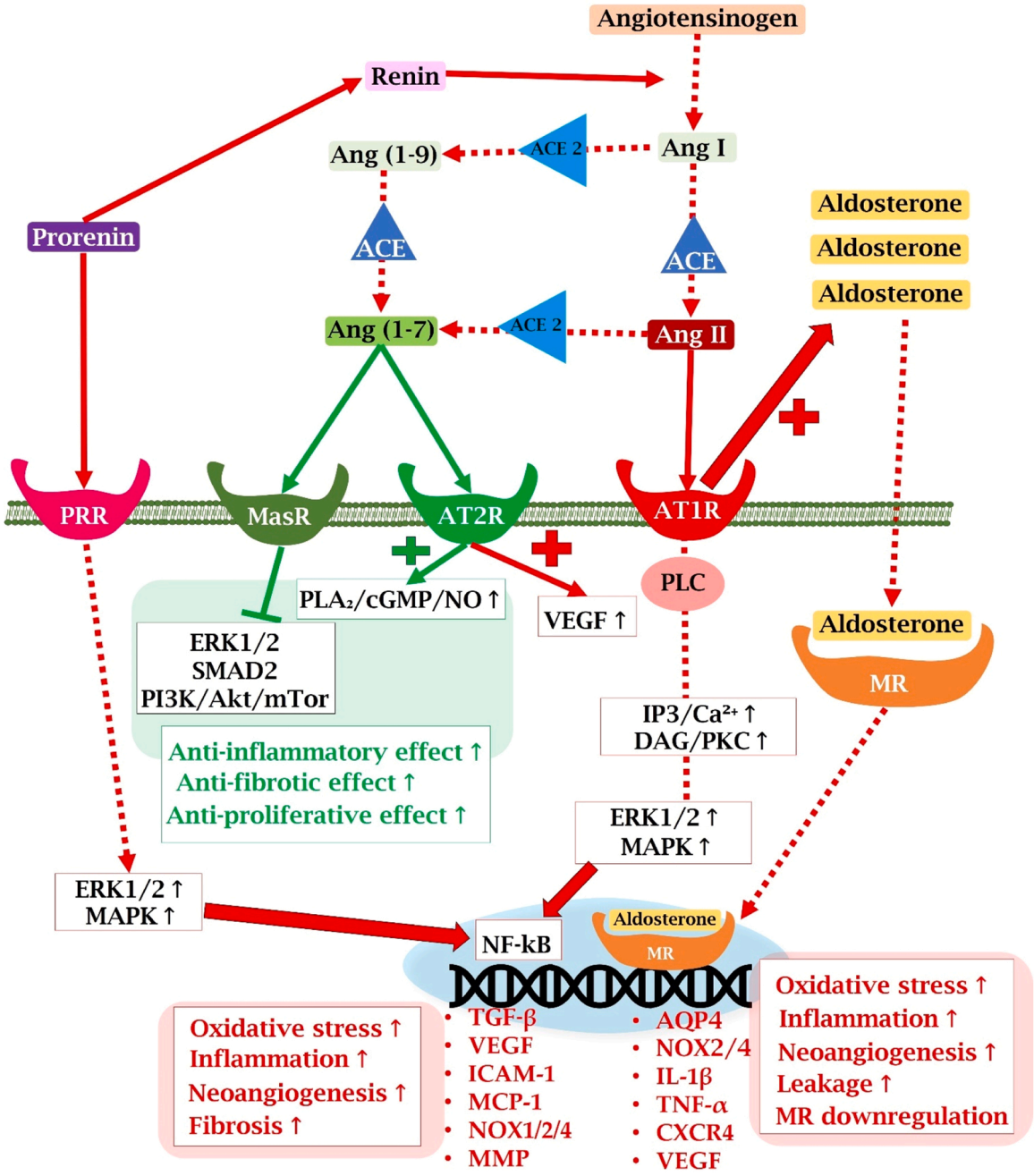

Fig. 2. Schematic representation of the mechanistic pathway of the RAAS and of the main intracellular cascades triggered by different ligands and receptors, components of the ocular RAAS. ACE: angiotensin-converting enzyme; Akt: Ak strain transforming (also known as protein kinase B); Ang: angiotensin; AQP4: aquaporin 4; AT1R: angiotensin II type 1 receptors; AT2R: angiotensin II type 2 receptors; cGMP: cyclic guanosine monophosphate; CXCR4: chemokine receptor type 4; DAG/PKC: diacylglycerol/protein kinase-C; ERK1/2: extracellular signal-regulated kinase 1/2; ICAM-1: intracellular adhesion molecule-1; IL-1β: interleukin 1β; IP3/Ca^{2+}: inositol-1,4,5-triphosphate/Calcium; MAPK: mitogen-activated protein kinase; MasR: Mas receptor; MCP-1: monocyte chemoattractant protein-1; MMP: matrix metalloproteinases; MR: mineralocorticoid receptor; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NO: nitric oxide; NOX: nicotinamide adenine dinucleotide phosphate oxidase; PI3K: phosphoinositide 3-kinase; PLA2: phospholipase A2; PLC: phospholipase C; PRR: (pro)renin receptor; SMAD2: suppressor of mothers against decapentaplegic type 2; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor α; VEGF: vascular endothelial growth factor.

2.4.2. *Cross-talk between the RAAS and the KKS*

The RAAS and KKS are closely interconnected through complex cross-talk involving multiple components from both systems [164–167]. Kallikrein not only generates kinins but also cleaves prorenin into renin, thus participating in both kinin-dependent and angiotensin-dependent signaling [153]. As previously discussed, ACE (or kininase II) plays a dual role: it catalyzes the conversion of Ang I to Ang II and also degrades kinins [164]. Additionally, ACE can process Ang (1−9) into Ang (1−7), which activates the AT2R, leading to BK generation and promoting vasodilation via the NO/cGMP axis [168]. Moreover, like ACE, also ACE2 can transform des-Arg^{9}-BK and des-Arg^{10}-KD into inactive metabolites [152,169]. Notably, Ang II, through AT1R activation, can upregulate B1R expression and activity by stimulating NOX and promoting pro-inflammatory mediators such as IL-1β and TNFα [170].

Taken together, the complex interconnections between the RAAS and the KKS have a pathophysiological relevance, and as such need to be

investigated to properly understand the influence of both these systems in the eye. Fig. 3 offers an overview of the mechanistic pathways of the KKS and its cross-talk with the RAAS.

2.4.3. The KKS in ocular pathophysiology

As extensively reported by Othman et al., growing evidence supports the significant involvement of the ocular KKS in the pathophysiology of several eye disorders, particularly in highly prevalent conditions such as DR and AMD [152]. Key components of the KKS, including the B1R and B2R and tissue kallikreins, have been identified in various ocular structures [171,172]. Notably, under conditions such as retinal hemorrhage, plasma kallikrein plays a central role in retinal dysfunction by mediating VEGF-driven effects [173,174]. In particular, B1R signaling is upregulated in specific retinal diseases. In fact, researchers have highlighted that B1R is highly expressed in endothelial cells and in the retinal pigment epithelium of human and rodent retina, indicating its possible involvement in the disruption of the blood–retinal barrier (BRB) during DR and AMD, possibly by suppressing tight junction constituents or by interfering with the cytoskeleton structure [152,160,175,176]. Additionally, in human endothelial cells, investigations have shown that B1R can trigger iNOS via the ERK pathway, therefore contributing to vascular inflammation [177]. Supporting its pathological role, Hachana et al. demonstrated that B1R blockade in a rodent model of AMD reduced both inflammation and vascular permeability [178].

Conversely, the role of B2R in retinal physiology and pathophysiology remains controversial [179,180]. While B2R signaling is essential for maintaining normal retinal vascular tone and blood flow, it has also been implicated in pathological neovascularization, particularly in animal models of oxygen-induced retinopathy [181].

Collectively, the existing literature underscores the pathophysiological role of plasma kallikrein and B1R in retinal neovascularization, further emphasizing the beneficial effect of KKS inhibitors to reduce retinal vascular permeability and inflammation. However, the precise

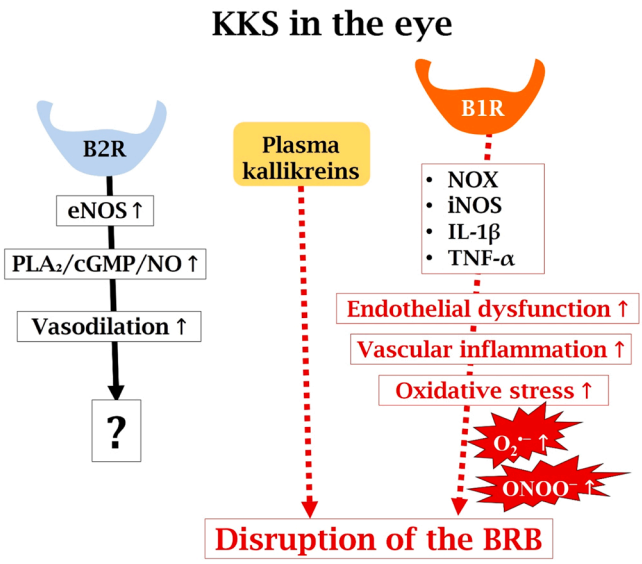

Fig. 4. Proposed model on the role of KKS in the ocular pathophysiology. B1R: bradykinin type 1 receptor; B2R: bradykinin type 2 receptor; BK: Bradykinin; BRB: blood-retinal barrier; cGMP: cyclic guanosine monophosphate; eNOS: endothelial nitric oxide synthase; IL-1 β: interleukin-1 β; iNOS: inducible nitric oxide synthase; KKS: kallikrein/kinin system; NO: nitric oxide; NOX: nicotinamide adenine dinucleotide phosphate oxidase; $O_2^{\bullet-}$: superoxide anion radical; $ONOO^-$: peroxynitrite; PLA_2: phospholipase A2; TNF-α: tumor necrosis factor α.

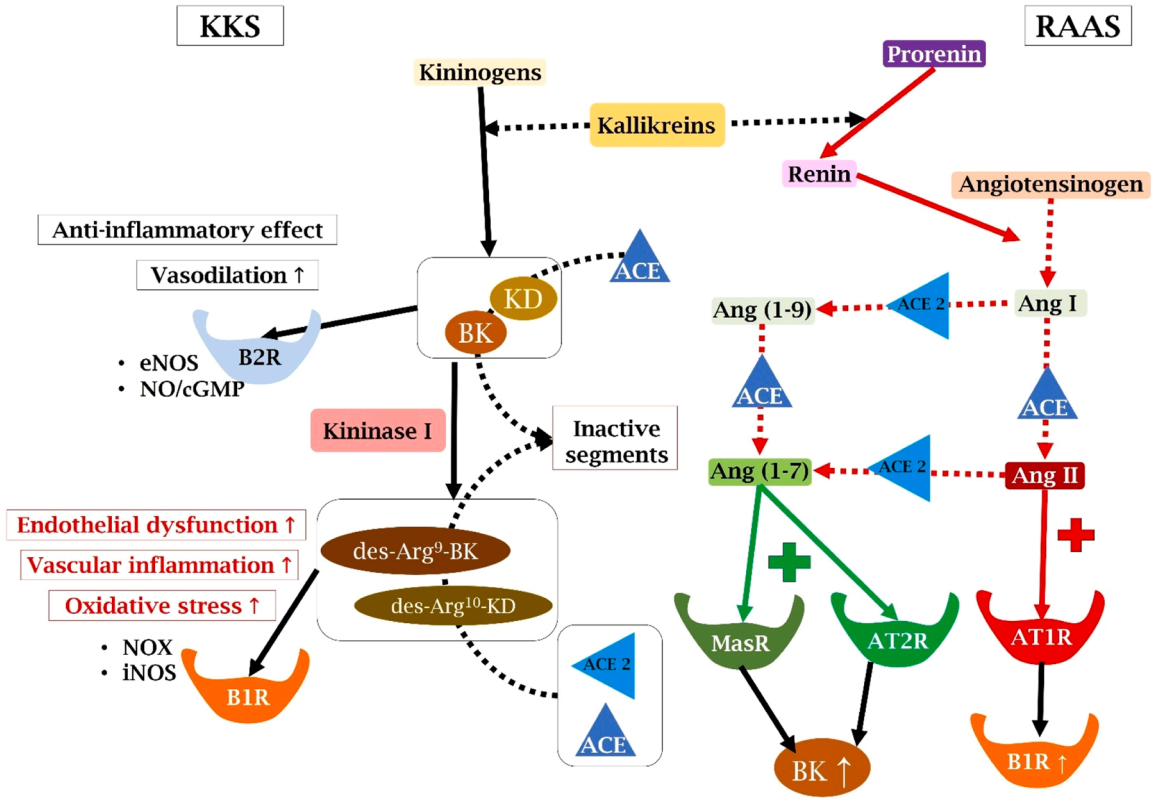

Fig. 3. Illustration of the mechanistic pathways of KKS and its cross-talk with the RAAS. ACE: angiotensin-converting enzyme; Ang: angiotensin; AT1R: angiotensin II type 1 receptors; AT2R: angiotensin II type 2 receptors; B1R: bradykinin type 1 receptor; B2R: bradykinin type 2 receptor; BK: Bradykinin; cGMP: cyclic guanosine monophosphate; eNOS: endothelial nitric oxide synthase; iNOS: inducible nitric oxide synthase; KKS: kallikrein/kinin system; MasR: Mas receptor; NO: nitric oxide; NOX: nicotinamide adenine dinucleotide phosphate oxidase; RAAS: renin-angiotensin-aldosterone system.

role of B2R signaling in the retina remains uncertain and requires further investigation [152]. Fig. 4 shows a schematic illustration of the plasma kallikrein effect as well as of B1R and B2R cascades in the eye.

3. The RAAS in individual ocular disorders

The following sections summarize current research on RAAS components in the eye, examining the pathophysiology of major ocular disorders, including glaucoma, cataract, DR, AMD, RVO, ROP, CSCR, ERM, and uveitis.

3.1. Glaucoma

3.1.1. General notions

Glaucoma refers to a group of disorders characterized by the progressive death of retinal ganglion cells, optic disc cupping, and a distinctive pattern of visual field defects [182]. It is one of the leading causes of irreversible visual loss worldwide, with elevated intraocular pressure (IOP) being a significant risk factor [183–186]. The elevated IOP is primarily due to increased outflow resistance, possibly as a consequence of remodeling in the trabecular meshwork (TM), a fundamental structure at the chamber angle. The increased aqueous humor outflow resistance subsequently causes a collapse of Schlemm's canal and compression of the TM, inducing a positive feedback loop that further increases IOP [187,188]. Hence, drugs reducing elevated IOP in glaucoma either diminish AH production or increase the trabecular and uveoscleral drainage routes.

While primary open-angle glaucoma (POAG) is associated with elevated IOP levels, one of its subtypes, normal tension glaucoma (NTG), does not involve elevated IOP, highlighting the importance of other risk factors such as arterial hypotension, abnormal autoregulation, endothelial dysfunction, autoimmunity, and oxidative stress in its pathogenesis [189].

Recent research has highlighted the role of neuroinflammation and disrupted redox homeostasis in glaucoma, highlighting the potential for novel therapeutic approaches. These include targeting immune signaling pathways using biologics or anti-cytokine agents such as etanercept, as well as mitigating ROS generation with antioxidants like resveratrol [190,191]. However, at the present, reducing IOP remains the most effective and widely adopted treatment strategy for glaucoma at present [192].

3.1.2. The RAAS in Glaucoma: insights into pathophysiology and pharmacological implications

We recently extensively reviewed the role of RAAS signaling pathways and respective treatment approaches in glaucoma [193]. Therefore, in the present chapter, we provide a concise overview on the recent findings of the RAAS in the context of glaucoma. Despite mixed findings on the impact of antihypertensive medications on the risk of IOP elevation and glaucoma onset [194,195], several studies have explored targeting the RAAS to combat glaucoma progression. Of note, untreated arterial hypertension has been linked to a higher risk of developing POAG, suggesting a potential association between systemic hypertension and glaucoma development [196]. In this context, the ocular RAAS may contribute to the regulation of AH formation and drainage, considering that RAAS components have been detected in ocular structures crucial for glaucoma pathophysiology, as demonstrated by in vitro studies on human non-pigmented ciliary epithelial cells [197]. Particularly, activation of the AT1R pathway increases AH production and secretion, modulating the uveoscleral outflow and consequently raising IOP [198–200]. Thus, suppression of RAAS, such as through ACE inhibition or AT1R blockade, may positively impact glaucoma management [201].

ACE inhibition prevents BK breakdown, induces prostaglandin generation, and ultimately lowers IOP by increasing uveoscleral outflow [202–205]. Moreover, ACE inhibitors reduce Ang II levels in AH, promoting uveoscleral outflow, and decrease blood flow in the ciliary body, reducing AH formation [206,207]. AT1R blockade has also been shown to enhance uveoscleral outflow. However, since both AH inflow and outflow remained stable in this study, the precise IOP-lowering mechanisms, beyond the increase in uveoscleral outflow, remain unclear [208]. It has been suggested that AT1R blockade reduces IOP by decreasing venous episcleral pressure, thereby facilitating trabecular outflow. Nevertheless, clinical studies on the IOP-lowering effects of losartan in hypertensive patients have found no correlation between systemic blood pressure and IOP reduction [209]. Additionally, vasoconstriction of the ocular vessels supplying the ciliary body, induced by Ang II, may elevate metabolic activity and promote AH production [210]. Importantly, IOP reduction via AT1R blockade has been shown to effectively protect against retinal ganglion cell loss [199,200,211,212].

Additionally, ACE2 and Ang (1–7), which primarily interact with the Mas receptor, promote vasodilatation, antiproliferative, and antifibrotic effects [213,214]. Consistent with this concept, studies have shown that the Mas receptor ligand Ang (1–7) and the ACE2 activator diminazene aceturate can reduce IOP, suggesting potential new approaches for glaucoma management [215–217]. Beyond its direct effects on AH production or outflow, the RAAS also influences the extracellular matrix (ECM) of the TM. Stimulation of the AT1R may increase the expression of growth factors, such as transforming growth factor β (TGF-β), thereby activating connective tissue growth factor (CTGF). This disruption of ECM homeostasis leads to ECM deposition through Wnt/β-catenin signaling and impaired bone morphogenetic protein (BMP) activity [218,219]. Furthermore, the inhibition of matrix metalloproteinases exacerbates ECM remodeling within the TM, contributing to elevated IOP in glaucoma [219]. These pro-fibrotic processes can be mitigated by enhancing the Ang(1−7)-Mas receptor axis [218].

Fig. 5 illustrates the primary mechanistic pathways through which RAAS components contribute to the pathogenesis of glaucoma, highlighting the corresponding potential therapeutic targets.

3.1.3. Recent advances: fibrogenesis, glial activation, and oxidative stress

Recent investigations have shed light on the pathogenic pathways triggered by Ang II, inducing oxidative and fibrotic processes in TM cells. An *in vitro* study by Li and colleagues on cultured human TM cells revealed that elevated levels of Ang II play a significant role in the pathophysiology of POAG by upregulating genes such as Col1, FN, and αSMA, encoding collagen type I, fibronectin, and alpha-smooth muscle actin, respectively, all involved in the fibrogenetic process. This occurs via a NOX4/ROS axis in cooperation with the Smad3/TGFβ pathway. Interestingly, a NOX4 inhibitor, GLX351322, was found to mitigate Ang II-related fibrogenesis [85]. Of note, after glaucoma filtration surgery, such as trabeculectomy or microstent implantation, the physiological AH drainage route is intentionally bypassed to reduce IOP [220]. Given the critical importance of preventing fibrosis in the Tenon's capsule to preserve the patency of this surgically created pathway, further research has explored the fibrotic response in this context. An *in vivo* study by Shi et al. in a rabbit model demonstrated that following trabeculectomy, increased levels of Ang II in Tenon's capsule fibroblasts led to events of fibroblast proliferation, migration, and phenotype transition to myofibroblasts, with an upregulation of genes like *FN* and *αSMA* [221]. Additionally, Kim et al. determined in an *in vitro* study on human Tenon fibroblasts that irbesartan, an AT1R blocker, effectively suppressed fibroblast migration and ROS production, further reducing cell number and morphologic alterations [222]. Subsequently, Ye et al. showed that isoliquiritigenin, a flavonoid with antioxidant activity [223], prevented Ang II-related fibrogenesis by blocking the NF-κB/PPARγ inflammatory pathway in human Tenon fibroblasts [224].

Fig. 6 provides a visual representation of the ocular structures implicated in the pathophysiology of POAG and presents an overview of the primary pathways addressing oxidative stress and RAAS dysregulation during POAG, particularly within the TM and Tenon's capsule after glaucoma filtration surgery.

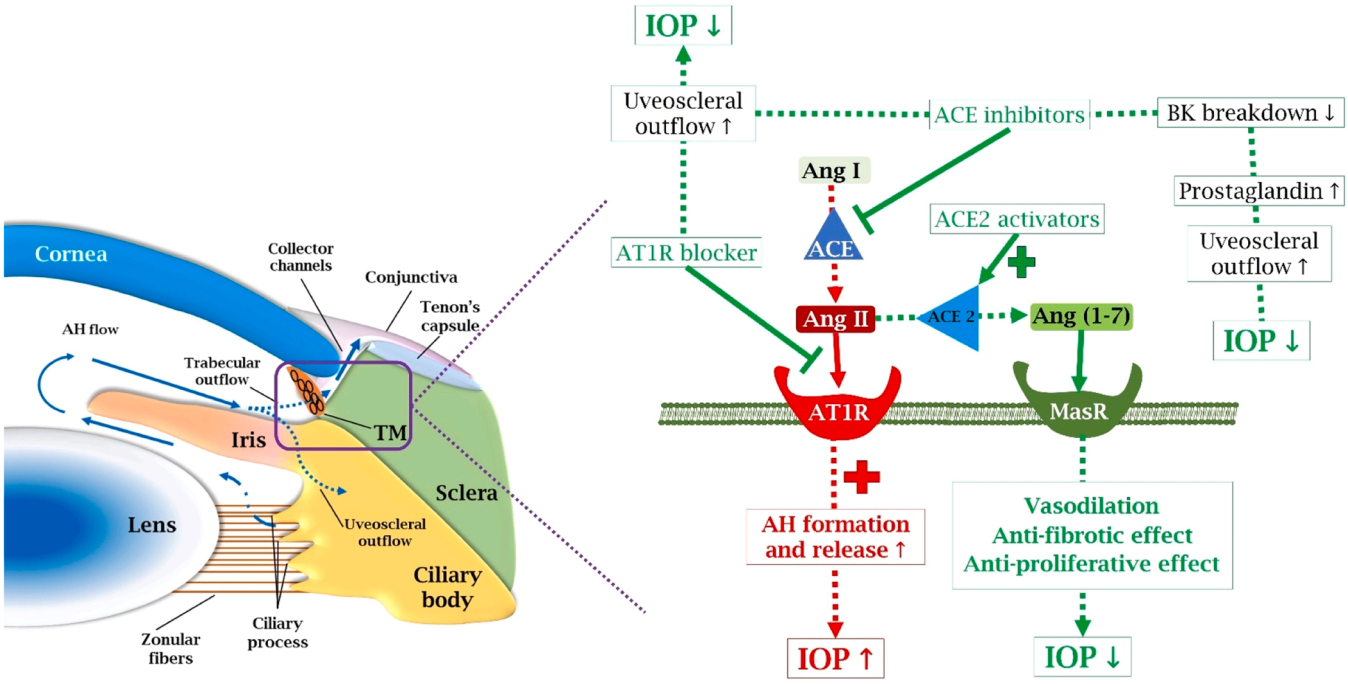

Fig. 5. Schematic representation of the mechanistic pathway of the RAAS contributing to increased IOP in glaucoma, alongside the mechanisms activated by RAAS modulators to mitigate IOP elevation. ACE: angiotensin-converting enzyme; Ang: angiotensin; AH: aqueous humor; AT1R: angiotensin II type 1 receptor; BK: bradykinin; IOP: intraocular pressure; MasR: Mas receptor; TM: trabecular meshwork.

Ang II also appears to play a crucial role in the pathogenesis of NTG. Notably, vascular endothelial dysfunction is considered a risk factor for NTG [225], and elevated Ang II levels were shown to trigger oxidative stress and endothelial dysfunction in ocular blood vessels via activation of the AT1R [7]. However, the AT1R was also shown to induce oxidative stress in retinal neurons and glia. For example, Ozawa et al. demonstrated that in cultured RGCs, oxidative stress induced cell death via the AT1R axis, which could be mitigated by telmisartan, an AT1R blocker [226]. Later, Semba and colleagues identified a pathogenetic AT1R–toll-like receptor (TLR)4– apoptosis signal-regulating kinase 1 (ASK1) pathway in Müller cells of a mouse model of NTG. This pathway contributed to the upregulation of inducible nitric oxide synthase (iNOS), triggering an oxidative stress-induced RGC death. However, candesartan could suppress the overexpression of iNOS and subsequent ROS excess by inhibiting the TLR4–ASK1 pathway, effectively protecting RGCs [227]. Moreover, studies employing systemic hypotensive drugs such as the ACE inhibitor, captopril, and the AT1R blocker, candesartan, suggest that systemic hypotension leads to increased renin production, subsequently elevating Ang II levels, which may adversely affect RGCs, inducing glial inflammation [228,229]. Given that vascular dysregulation and hypotension are recognized risk factors for NTG, Jeon et al. investigated renin and Ang II levels in NTG patients and control subjects, revealing significantly higher systemic concentrations and variability of renin in NTG individuals [230]. Further research by the same group compared glaucoma models of ocular hypertensive rats with a model of systemic hypotensive rats, revealing higher levels of Ang II and receptors in both serum and retina of systemic hypotensive rats. These rats also exhibited glial activation and, importantly, events of necroptosis in RGCs via elevated tumor necrosis factor α (TNF-α), receptor-interacting protein 3 (RIP3), and decreased inactive caspase 8 [231]. Interestingly, the described axis involving Ang II, glial activation, and associated RGC necroptosis was specific to systemic hypotension, as JNK and RIP3 inhibitors could reverse RGC death in hypotensive but not hypertensive rats [231]. Furthermore, Oh and colleagues recently demonstrated in a systemic hypotensive rat model that both AT1R and AT2R expression increased in the sclera after systemic hypotension, along with elevated levels of TGF-β1, TGF-β2, αSMA, and collagen type I, indicating activation of scleral fibroblasts and their differentiation into myofibroblasts [232]. The authors also found a correlation between fibroblast activation and RGC death, which was reversed by sub-Tenon injection of the AT1R blocker, losartan, suggesting that inhibition of Ang II may suppress scleral fibrogenesis, ultimately protecting RGCs [232]. Fig. 7 provides an overview on the retinal layers and shows the involvement of RAAS in glial activation and RGC loss in NTG.

Several clinical studies have explored the role of the RAAS and its inhibitors as potential therapeutic strategies for glaucoma. Findings from the Gutenberg Health Study, which analyzed the impact of cardiovascular medications on IOP, initially showed a positive association between IOP and the use of ACE inhibitors and angiotensin receptor blockers. However, after adjusting for systolic blood pressure and central corneal thickness relative to body mass index (BMI), this correlation was no longer significant, suggesting that systemic conditions such as obesity may have a stronger influence on IOP than RAAS activity itself [233]. Overall, evidence regarding the use of RAAS inhibitors in glaucoma remains inconsistent [234]. While some studies have indicated that these agents may slow disease progression, particularly in older patients, others have failed to confirm these benefits [234–236]. Notably, treatment with losartan lowered blood pressure in hypertensive patients with or without glaucoma but had no such effect in normotensive individuals, implying a low risk of systemic hypotension when RAAS inhibitors are used in normotensive glaucoma patients [209]. Despite these insights, randomized controlled trials specifically targeting individuals with glaucoma are still lacking. Future studies are essential to clarify the potential therapeutic value of RAAS inhibition in glaucoma management.

In summary, recent findings on the potential for blocking the RAAS in glaucoma have illuminated pathogenetic events such as fibrogenesis, relevant in wound healing post-glaucoma filtration surgeries, glial activation, inflammation, and the establishment of oxidative stress. These processes can be effectively countered by molecules like the antioxidant flavonoid isoliquiritigenin, ACE inhibitors like captopril, or AT1R blockers such as losartan or candesartan. However, these recent

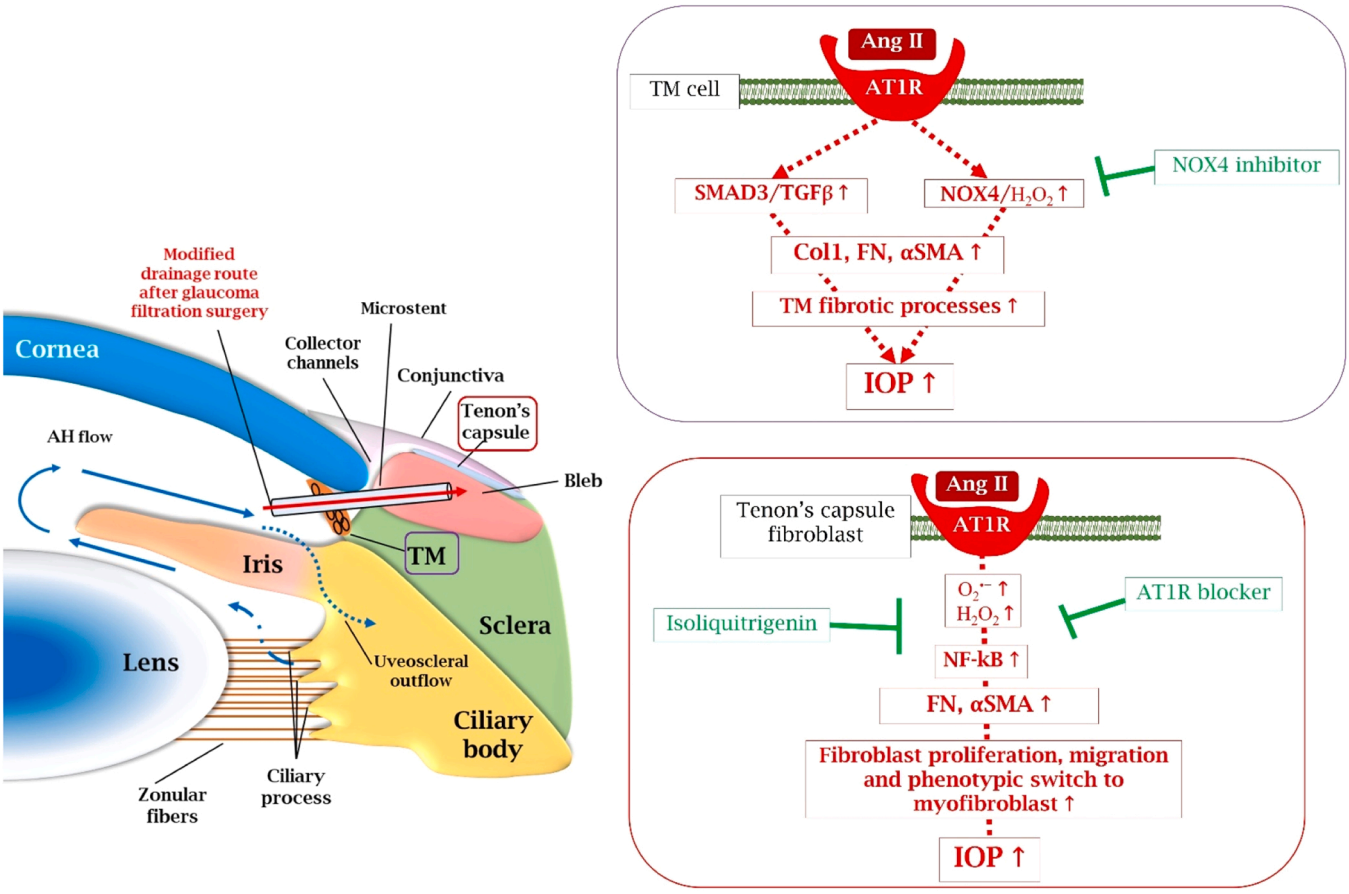

Fig. 6. Schematic representation of the primary ocular structures involved in the pathogenesis of glaucoma, alongside an illustration of the mechanistic pathways of RAAS modulators and antioxidants aimed at counteracting oxidative stress and elevated IOP during POAG within the TM and Tenon's capsule after glaucoma filtration surgery. αSMA: α-smooth muscle actin; Ang: angiotensin; AQ: aqueous humor; AT1R: angiotensin II type 1 receptors; Col1: collagen type 1; FN: fibronectin; H_2O_2: hydrogen peroxide; IOP: intraocular pressure; NF-kB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NOX: nicotinamide adenine dinucleotide phosphate oxidase; $O_2^{\bullet-}$: superoxide anion radical; SMAD3: suppressor of mothers against decapentaplegic type 3; TGF-β: transforming growth factor β; TM: trabecular meshwork.

pre-clinical investigations require further exploration to confirm the results and potentially validate these novel treatment strategies for large clinical studies.

3.2. Cataract

3.2.1. General aspects

Lens opacification, also known as cataract, is a leading cause of blindness worldwide. In 2020, out of more than 43.3 million people who were blind worldwide and 295 million affected by moderate-to-severe visual impairment, approximately 17.0 million (39.6 %) cases of blindness and 83.5 million (28.3 %) cases of moderate-to-severe visual impairment were attributed to cataracts [237]. Cataract is a multifactorial condition. While sex and genetics play roles in cataractogenesis, the primary pathophysiological drivers are aging and oxidative stress [238–240]. Additionally, cataractogenesis is associated with specific pathological conditions such as diabetes, obesity, and arterial hypertension [241].

From a pathophysiological perspective, aging reduces the efficiency of physiological lens transport systems and decreases endogenous antioxidant enzymatic activity. This leads to a reduced production of water-soluble crystallins and an accumulation of water-insoluble proteins [241]. In this context, oxidation, crystallin destabilization, and protein misfolding collectively cause lens opacification, ultimately resulting in cataract formation [242]. Therapeutically, the primary treatment strategy remains the surgical extraction of the cataractous lens, followed by the implantation of an artificial intraocular lens [243]. However, in recent years, experimental pharmacological treatments, such as those based on antioxidants, have been tested with the aim of reversing cataracts [244]. These efforts are driven by the global prevalence of this disorder and the need to develop new therapeutic strategies to address the global deficit in surgery access and resources [244].

3.2.2. The RAAS in cataractogenesis: role of oxidative stress

Past and recent studies on the impact of antihypertensive agents on cataract formation and progression have yielded controversial results [245–248]. However, current literature suggests a link between hypertension, oxidative stress, and cataract formation [249,250]. Arterial hypertension is associated with overactivation of the RAAS [251], which, at the local level within the lens, has been shown to suppress Na^+/K^+-ATPase pump activity. This disruption of the ion gradient in the lens epithelium can lead to lenticular swelling, thereby contributing to cataractogenesis [252]. In hypertensive rats, decreased Ca^{2+} ATPase activities and a significant reduction in endogenous antioxidants like SOD and GSH were observed, which could be reversed with ramipril administration, leading to reduced blood pressure [253]. A study conducted on albino rats revealed that chronic administration of cadmium chloride ($CdCl_2$), a compound known to induce hypertension, also triggers cataractogenesis. The underlying mechanism appears to involve increased oxidative stress, characterized by decreased levels of key antioxidant enzymes such as GPO, SOD, and GSH, in both the serum and the eye lens of of hypertensive rats. This imbalance leads to elevated

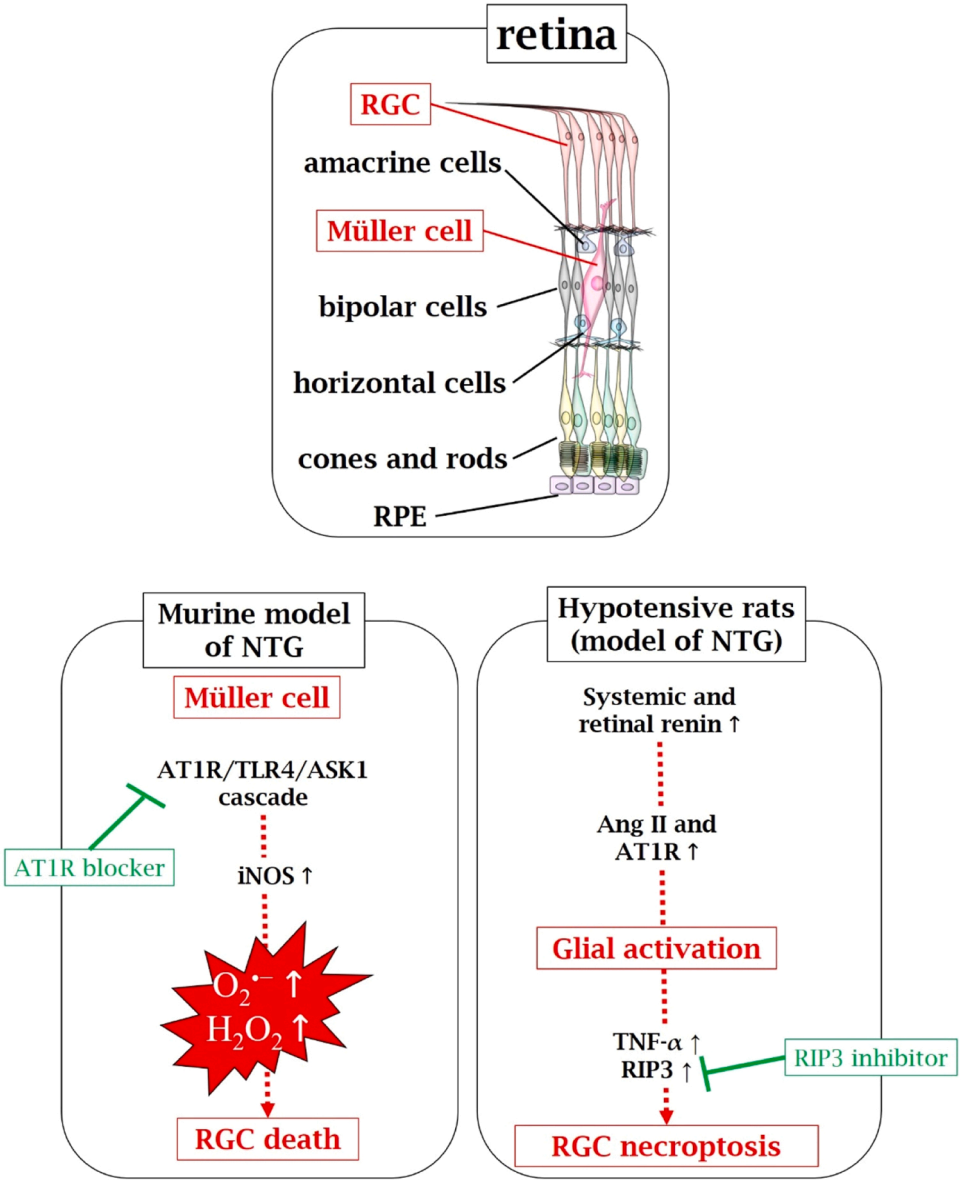

Fig. 7. Schematic representation of the retinal layers, and illustration of the mechanistic pathways involving RAAS components in glial activation and RGC loss during NTG. Ang: angiotensin; ASK1: apoptosis signal-regulating kinase 1; AT1R: angiotensin II receptor type 1; H_2O_2: hydrogen peroxide; iNOS: inducible nitric oxide synthase; NTG: normal tension glaucoma; $O_2^{\bullet-}$: superoxide anion radical; RIP3: receptor interacting protein 3; RGC: retinal ganglion cell; RPE: retinal pigment epithelium; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor α.

ROS levels, which damage lens proteins and phospholipids, promote lipid peroxidation, and further exacerbate the oxidative-antioxidant imbalance [253]. Furthermore, the accumulation of Na^+ and Ca^{2+} contributes to lenticular protein aggregation, resulting in lens opacity and cataract development. Elevated Ca^{2+} levels also stimulate proteolysis in lens epithelial cells, further advancing opacification—an essential step in cataractogenesis [254]. Previous research has implicated the ocular RAAS in exacerbating cadmium-related hypertension and its associated toxicity [255]. Building on this knowledge, Choudhary and Bodhake demonstrated that olmesartan, an Ang II receptor blocker, effectively suppressed cataract progression in an albino rat model of $CdCl_2$-induced hypertension. This protective effect was attributed to preserved antioxidant enzyme levels, reduced oxidative stress, and the restoration of protein content, ion balance, particularly Na^+ and Ca^{2+}, and ATPase activity in the lens [256]. Further research on hypertensive rats has shown that olmesartan effectively counteracted the RAAS and cataractogenesis, restored redox homeostasis, and enhanced antioxidant activities, indicating that the ocular RAAS significantly increases lenticular oxidative stress, leading to cataractogenesis [21]. Apart from arterial hypertension, diabetes mellitus is another condition that promotes cataract formation. Chronic hyperglycemia activates the polyol pathway, leading to sorbitol accumulation in the lens, causing osmotic stress, ROS overproduction, and apoptosis of LECs [257–261]. Notably, chronic hyperglycemia is also linked to RAAS overactivation [262,263]. Interestingly, an investigation has demonstrated that losartan, another Ang II receptor blocker, effectively slows the progression of diabetic-induced cataracts in albino rats, suggesting that RAAS modulators counteract cataractogenesis by reducing oxidative stress, independent of blood pressure levels [264]. Supporting this hypothesis, studies on streptozotocin-induced diabetic rats demonstrated that candesartan effectively mitigates oxidative stress and cataractogenesis. These studies found a positive correlation between ACE levels and pro-oxidative agents (NOX1, NOX4, iNOS) and a negative correlation between ACE and the antioxidant enzyme SOD, linking diabetic cataract

pathogenesis to increased focal ACE and Ang II levels in the lens, promoting oxidative factors [86].

Another investigation on hyperglycemia-related cataracts in Sprague Dawley rats, using a recognized streptozotocin-induced diabetic model, reported that various RAAS modulators (aliskiren, a direct renin inhibitor; enalapril, an ACE inhibitor; olmesartan; and ang 1–7) reduced lenticular opacity, restored antioxidant levels, and decreased ROS levels, collectively diminishing cataract formation and confirming the connection between oxidative stress and cataractogenesis [265]. Consistent with these findings, a study focused on the topical administration of enalapril in a hypertensive cataract model reported beneficial effects in combating cataractogenesis by inhibiting the upregulated ocular RAAS and reducing oxidative stress by restoring the levels of antioxidants, MDA, and nitrite [266].

In summary, recent experimental works indicate that RAAS modulators show promise in counteracting hypertensive and diabetic-related cataractogenesis by restoring redox homeostasis, highlighting a significant link between the RAAS, oxidative stress, and cataract formation. However, despite these promising preclinical results, translation into clinical practice remains limited. Future randomized clinical trials are needed to further investigate the therapeutic potential of RAAS modulation in cataract prevention and treatment. Nonetheless, such studies are inherently challenging due to the multifactorial nature of cataractogenesis, particularly in elderly, often multimorbid populations, where numerous confounding variables complicate study design and interpretation.

Fig. 8 illustrates the central pathogenetic events and the reported therapeutic strategies potentially able to counteract cataractogenesis by targeting the ocular RAAS.

3.3. Diabetic retinopathy

3.3.1. General concepts

DR is a progressive, highly prevalent, and severe retinal microvascular disease, recognized as a common ocular complication of diabetes mellitus [267]. Currently, over 400 million individuals worldwide are affected by diabetes, with more than 30 % of these patients presenting with DR [268]. The primary factor influencing the onset and the progression of DR is blood glucose control. Additionally, arterial hypertension and blood lipid levels are significant risk factors [269]. DR is divided into two subtypes based on disease progression and severity: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The key distinction between these forms is the presence of extensive retinal neovascularization in PDR [270,271].

The main pathological changes in DR include the loss of pericytes, increased vascular permeability, and basement membrane thickening. These changes lead to the narrowing of the capillary cavity, reducing retinal perfusion. Consequently, the retinal tissue becomes ischemic and hypoxic, stimulating the release of neoangiogenic factors. This results in a dramatic process of neovascularization, causing neural damage and vision loss in the affected retina [272,273]. Given the primary roles of oxidative stress and inflammation in triggering neovascularization and increased vascular permeability, recent decades have seen a growing body of research focusing on testing antioxidants and immunomodulators to manage DR [274].

3.3.2. The RAAS and diabetic retinopathy: pharmacological implications

Hyperglycemia fundamentally induces an upregulation of the RAAS. Studies have shown that high blood glucose levels increase renin synthesis due to the accumulation of succinate and its receptor, the G protein-coupled receptor 91 (GPR91). Specifically, in DR, excess succinate activates GPR91 via an ERK1/2/cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) signaling pathway, leading to the upregulation of VEGF [275]. This also triggers the activation of iNOS, releasing NO, which supports renin synthesis [276]. Consequently, numerous studies have revealed a relationship between RAAS activity and the occurrence of DR. A Canadian study on diabetic patients aged 50 and above indicated that individuals with PDR observed an overactivation of the RAAS in the peripheral vascular system [277]. Other studies have also reported elevated levels of Ang II and angiotensinogen in DR, suggesting the potential of targeting RAAS components to combat DR [55,278,279]. Large clinical investigations like the DIRECT-Protect and the DIRECT-Prevent trials assessed the effectiveness of candesartan in preventing the development or progression of diabetic retinopathy, concluding that while the drug reduced the onset of DR, it had no significant effect on disease progression [280].

Mechanistically, Ang II promotes neovascularization by inducing overexpression of retinal VEGF. A study on patients affected by PDR reported increased Ang II levels in the vitreous, correlating positively with VEGF levels [281]. Additionally, ACE inhibitors and AT1R blockers have been shown to protect against DR by reducing VEGF overexpression in the retina [282,283]. Ang II also influences pericyte loss, an early pathogenetic event in DR [284], as evidenced by a study on bovine retinal cells demonstrating that AT1R signaling stimulates retinal microvascular pericyte migration [285]. Moreover, Ang II can induce pericyte apoptosis via α3 and β1 integrin intracellular signaling [286]. In

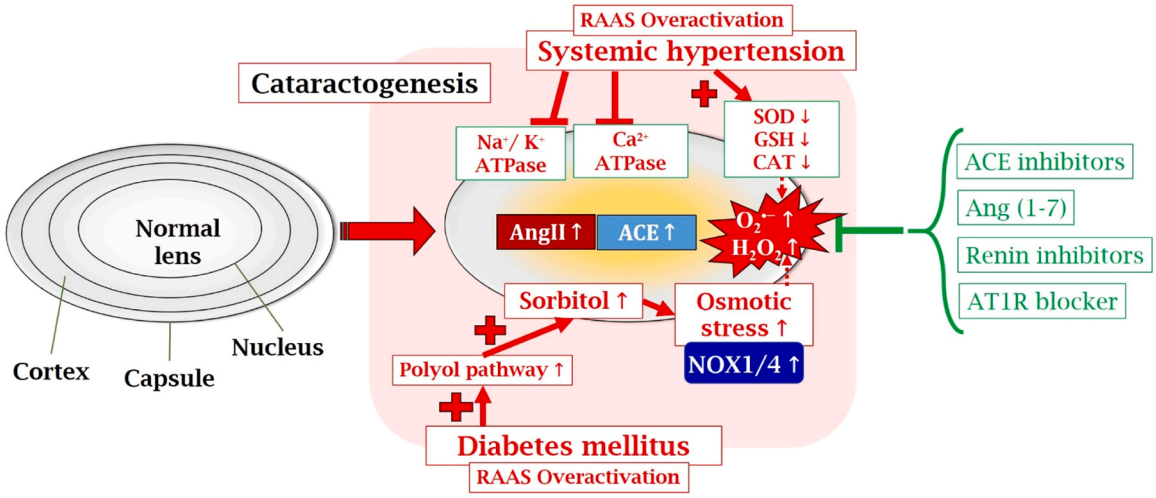

Fig. 8. Schematic representation of the mechanistic cascades of cataractogenesis, role of oxidative stress and actions of RAAS modulators in contrasting the formation of cataract. ACE: angiotensin-converting enzyme; Ang: angiotensin; AT1R: angiotensin II receptor type 1; ATPase: adenosine triphosphatase; CAT: catalase; GSH: glutathione; H_2O_2: hydrogen peroxide; NOX: nicotinamide adenine dinucleotide phosphate oxidase; $O_2^{\bullet-}$: superoxide anion radical; SOD: superoxide dismutase.

addition to Ang II, aldosterone plays a role in DR pathogenesis. In a mouse model of ischemic retinopathy, aldosterone exposure caused retinal edema and extensive retinal hemorrhages, along with Müller cell dysfunction and mononuclear phagocyte infiltration [287]. A mineralocorticoid receptor antagonist, finerenone, reduced vascular leakage and microglial/macrophage density in a rodent model of DR, decreasing levels of VEGF, ICAM-1, and IL-1β [20]. Prorenin and its receptor (P)RR signaling are also implicated in DR pathogenesis. In fact, studies have reported that prorenin concentrations in plasma and vitreous of patients with diabetes are increased [288], suggesting that prorenin is a powerful driver of microvascular complications in diabetes [289,290]. Mechanistically, (P)RR is responsible for VEGF/VEGR2 and TGF-β1 upregulation via the ERK1/2 pathway [135,291,292]. In this context, Satofuka et al. have shown that PRR inhibitors can reduce VEGF overexpression and decrease retinal leukocyte adhesion in AT1-R–deficient diabetic mice [291]. Additionally, ACE activates TGF-β1/Smad signaling, which is involved in blood-retina barrier destruction during DR [293]. Conversely, ACE2 appears to have beneficial effects, preventing or reversing DR [19], and reducing RGC loss [294].

Overall, the RAAS regulates hemodynamic changes through key

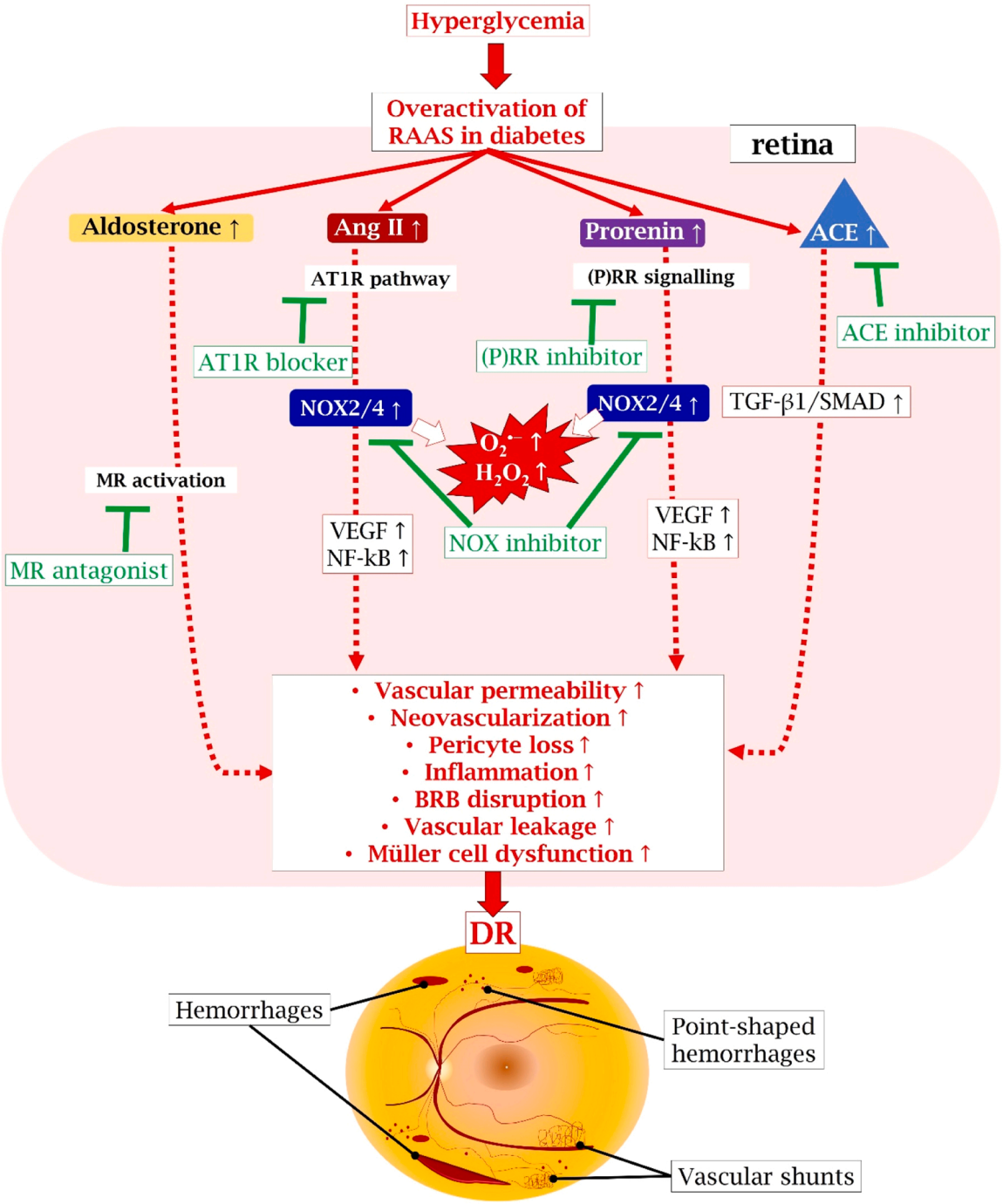

Fig. 9. Overview on the involvement of RAAS in the pathophysiology of DR. ACE: angiotensin-converting enzyme; AT1R: angiotensin II type 1 receptors; DR: diabetic retinopathy; IL-1β: interleukin 1β; H_2O_2: hydrogen peroxide; MR: mineralocorticoid receptor; NF-κB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NOX: nicotinamide adenine dinucleotide phosphate oxidase; $O_2^{\bullet-}$: superoxide anion radical; PRR: (pro)renin receptor; SMAD: suppressor of mothers against decapentaplegic type; TGF-β1: transforming growth factor-β 1; VEGF: vascular endothelial growth factor.

mediators such as Ang II, aldosterone, and prorenin, causing damage to retinal endothelial cell function and pericytes, promoting VEGF upregulation, and leading to neovascularization in DR.

Studies have reported that Ang II and aldosterone increase microglial density and stimulate the overproduction of ROS and neovascularization in the retina of animal models. Their antagonists, however, reverse these effects [295,296]. Activation of the RAAS leads to ROS formation, increasing vascular permeability and damaging retinal cells, thereby contributing to DR [297]. For example, telmisartan treatment in diabetic retinas increased endogenous GSH levels, enhancing neurotrophic support and reducing signs of retinal cell apoptosis [298]. Experimental results also indicate that AT1R blockers effectively mitigate ocular inflammatory responses and oxidative stress caused by diabetes, reducing levels of inflammatory and pro-oxidative agents such as VEGF, NF-κB, ICAM-1, and NOX [14,283,299,300]. In diabetic animal models, Ang II has been shown to trigger inflammation, neovascularization, and oxidative stress. For example, in a diabetic rodent model, Ang II infusion raised levels of VEGF and p22phox, a subunit of NOX1/2/4, in the retina. These effects were reduced with the administration of candesartan, an AT1R blocker [87]. Further, a study on diabetic rats by Chen and colleagues revealed that Ang II induces retinal leukostasis, mediated by the upregulation of NOX and VEGF. This process could be reversed by apocynin, a NOX inhibitor [88]. Additionally, Haque and associates demonstrated in human RPE cells that hyperglycemia upregulates VEGF expression and NOX activation via (P)RR signaling, independently of Ang II, which could be reversed with NOX inhibitors [95].

These emerging findings have been supported by several clinical studies demonstrating the beneficial effects of ACE inhibitors and AT1R blockers in managing DR. A meta-analysis revealed that the use of RAAS modulators mitigates the risk of DR progression and increases the likelihood of retinopathy regression, particularly in normotensive individuals [301]. Particularly, the literature underscores a protective effect of RAAS modulators in patients affected by mild to moderate DR [302]. For example, while candesartan did not significantly slow DR progression, it was associated with a reduced incidence of new-onset DR [303]. Moreover, the incidence of adverse events was comparable between the candesartan and placebo groups, suggesting that candesartan is generally safe for use in diabetic patients [303]. Despite the availability of randomized clinical trials investigating RAAS inhibitors as a therapeutic option for DR, the presence of comorbidities, such as hypertension and obesity, common in diabetic populations, complicates the interpretation of these findings.

In summary, the RAAS significantly contributes to the pathogenesis of DR through oxidative stress, neovascularization, and inflammation. Fig. 9 presents a schematic overview of the main pathomechanisms involving the RAAS, oxidative stress, and neovascularization in DR.

3.4. Age-related macular degeneration

3.4.1. General aspects

Age-related macular degeneration (AMD) is a leading cause of blindness in people over 50. A Global Burden of Disease study on AMD has estimated that in 2020, globally over 1.85 million individuals were blind due to AMD, while 6.23 million people presented moderate-to-severe visual impairment [304]. With the increasing average life expectancy, the impact of AMD on the health care system is expected to grow [305]. The pathogenesis of AMD is complex and influenced by various metabolic, functional, genetic, and environmental risk factors, including a high fat diet, sunlight exposure, mitochondrial DNA polymorphisms, and smoking [306–309]. Central to the pathogenesis of AMD are oxidative stress and vascular dysfunction [310–312]. AMD involves degeneration of the central retina, including impaired function of photoreceptors, the retinal pigment epithelium (RPE), Bruch's membrane, and the choriocapillaris. This degeneration leads to the accumulation of macular drusen, which are typical retinal deposits. As the disease progresses, RPE atrophy occurs, accompanied by choroidal neovascularization (CNV) [313]. Clinically, AMD is differentiated into non-neovascular and neovascular stages. Non-neovascular AMD is characterized by macular drusen, appearing as yellow deposits within the macula. Geographic atrophy represents the terminal stage of non-neovascular AMD, causing severe vision loss when the fovea is involved. Progressive RPE atrophy can lead to CNV, marking the transition to neovascular AMD. CNV and increased VEGF expression cause fluid leakage into the intraretinal and subretinal spaces, as well as hemorrhages, resulting in rapid and severe vision loss. Inflammation and oxidative stress can exacerbate this process [314]. The standard therapy for neovascular AMD involves intravitreal injections of anti-VEGF agents. Monthly administration of bevacizumab, ranibizumab, or aflibercept has been shown to improve visual acuity and reduce central retinal thickness, as observed in optical coherence tomography [315,316]. Recent clinical studies have introduced faricimab, a dual inhibitor of angiopoietin-2 and VEGF, as another potent treatment option for neovascular AMD. Faricimab has demonstrated visual benefits and the potential for extended treatment regimens [317].

3.4.2. The RAAS in AMD: pharmacological targets

Inflammation and oxidative stress are key factors that exacerbate the progression of neovascular AMD. Due to its high oxygen consumption, the retina generates elevated levels of ROS, and an imbalance between antioxidant capacities and ROS generation leads to RPE cell death and the release of inflammatory cytokines [314]. Several components of the RAAS are expressed in ocular tissues, and studies have explored the role of RAAS dysregulation in AMD pathogenesis. Arterial hypertension, often associated with excessive RAAS activation, is identified as a systemic risk factor for AMD [318]. Ang II is a major effector hormone in the pathogenesis of arterial hypertension. A characteristic feature of AMD is the deposition of lipid-rich ECM under the RPE. Ang II binding to the AT1R receptor increases the activity of matrix metalloproteinases (MMP)-2 and MMP-14 via an MAPK pathway, specifically through ERK/p38 signaling in the RPE, leading to a dysfunctional RPE basement membrane and aggravation of subretinal ECM deposits [319,320]. Praddaude et al. reported that Ang II infusion in mice upregulated AT1a and AT1b receptor expression, elevated intracellular calcium concentration, increased MMP-2 activity, and led to collagen IV accumulation, effects reversible by Ang II receptor blockers [321]. Moreover, studies have suggested that sub-RPE deposits formed in response to oxidative damage may require an additional injury for these accumulations to traverse the RPE basement membrane, indicating as a possible second injury for the effects of Ang II on the RPE [319,321]. Ang II also significantly contributes to oxidative stress in RPE cells via the upregulation of NOX. In particular, studies have demonstrated that downregulating the p22phox subunit of NOX 1, 2, and 4 decreases ROS formation and inflammatory cytokine production by suppressing MAPK and NF-κB pathways, counteracting Ang II-induced oxidative stress in RPE cells, and benefiting against CNV [89,90]. In this context, Pulgar et al. found that human angiotensinogen is internalized by RPE cells and localized in the nucleus and mitochondria, possibly stimulating oxidative stress via NOX, an effect reversible by the NOX1/4 inhibitor GKT137831 [91]. Another investigation by Fu and co-workers has shown that an Nrf2 activator, the 4-octyl itaconate [322], effectively counteracts Ang II-induced oxidative stress in human RPE cells, reducing ROS generation and pro-inflammatory cytokines like IL-8, and IL-6 [323].

Recently, the RAAS has also been linked to the accumulation of oxidized low-density lipoproteins (ox-LDL) in macrophages in high-fat diet-fed mice. This accumulation, induced by AT1R signaling, disrupts cholesterol efflux, leading to macrophage activation, inflammation, and visual impairment. The accumulation of ox-LDL in these macrophages was induced by AT1R signaling and disturbance of the downstream ELAVL1/PPARγ/ATP-binding cassette transporter (ABCA1) axis caused dysfunctional cholesterol efflux in these macrophages. Moreover, ox-LDL accumulation stimulated the release of inflammatory cytokines,

such as IL-1β, TNF-α and VEGF. All these effects, associated with AMD disease progression, could be reduced by AT1R blockade [15]. Blockade of AT1R upregulates ABCA1, a key component of the cholesterol efflux system[15]. In ABCA1-deficient macrophages, higher CNV volumes were detected compared to controls, indicating a VEGF-independent pro-angiogenic phenotype [324]. Prorenin and its receptor (P)RR also play roles in AMD pathogenesis. In a murine model of laser-induced CNV, (P)RR blockade reduced CNV development and the expression of intercellular adhesion molecule-1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1), VEGF, VEGF receptor (VEGFR)-1, and VEGFR-2 [325]. The development of a new single-stranded RNAi agent targeting human and mouse (P)RR allowed for the analysis of its therapeutic effect against laser-induced CNV and subretinal fibrosis. Administration of this agent lead to significantly reduced CNV formation, decreased expression of inflammatory molecules and macrophage infiltration. Furthermore, subretinal fibrosis and epithelial-mesenchymal transition (EMT)-related markers, such as phosphorylated SMAD2, were diminished. These effects were comparable to treatment with the anti-VEGF agent aflibercept [326].

Other studies have demonstrated the importance of AT1R-mediated inflammation in the development of CNV. Blockade of the AT1R with telmisartan decreased macrophage infiltration and the upregulation of VEGF and inflammatory cytokines in the RPE-choroid complex, leading to a significant reduction in CNV volume [327]. In a rat model of laser-induced CNV, subconjunctival injections of candesartan, an AT1R blocker, significantly reduced CNV volume and inflammation [328].

Photoreceptor degeneration and choroidal neovascularization are associated with the accumulation of activated mononuclear phagocytes in the subretinal space. Recently, it has been demonstrated that Ang II mobilizes AT1R-positive splenic monocytes to infiltrate the chorioretinal tissue, promoting pathologic CNV formation. AT1R antagonists and splenectomy reversed subretinal mononuclear phagocyte accumulation, CNV formation, chronic retinal inflammation, and cone degeneration in aged AMD-risk ApoE2-expressing mice [329]. In the same study, elevated plasma renin activity and equilibrium angiotensin II were detected in patients with AMD compared to control plasma samples, indicating a potential link between systemic activation of RAAS and AMD [329]. This suggests that RAAS inhibition has high potential

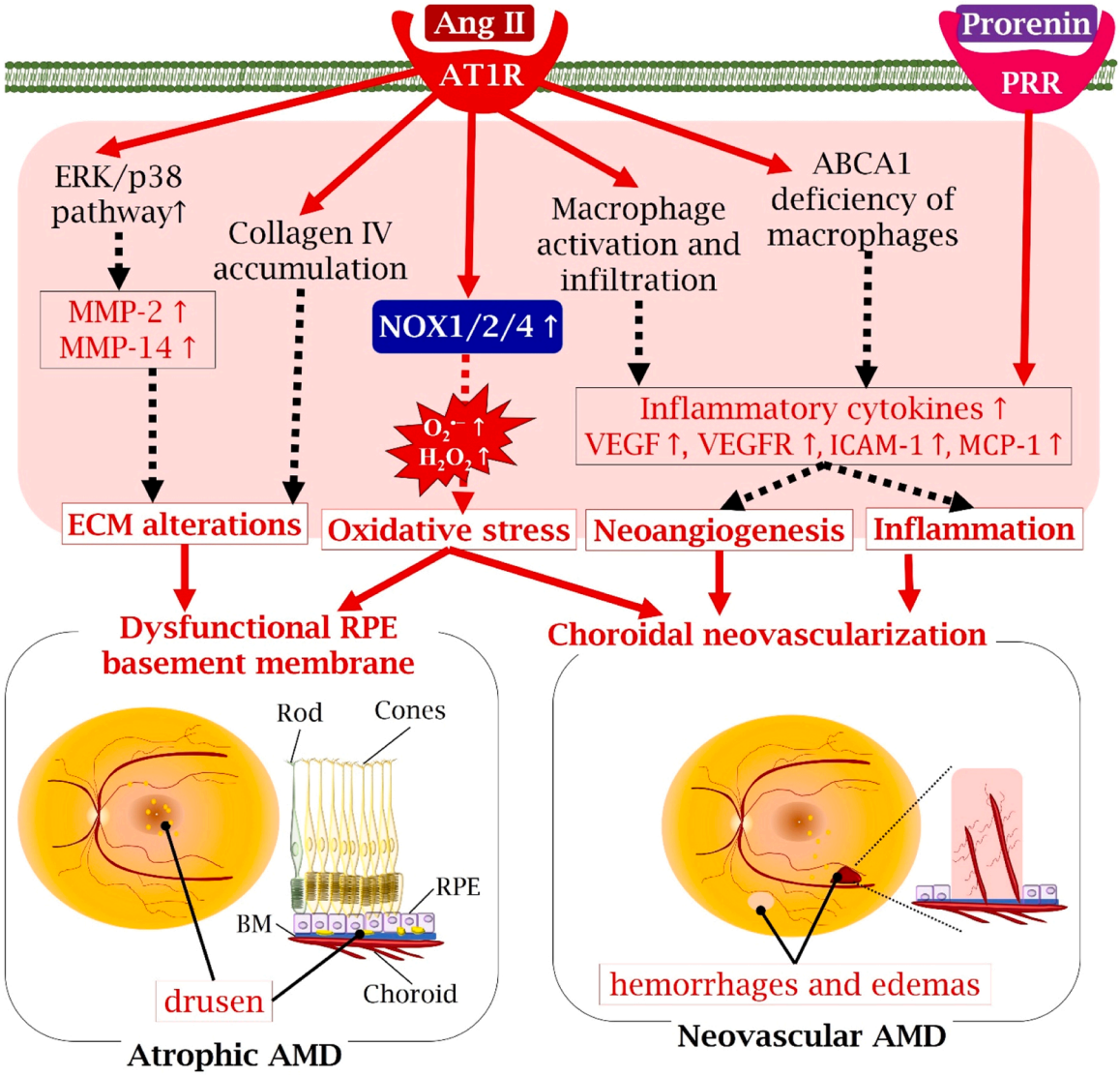

Fig. 10. Schematic illustration on the involvement of the ocular RAAS into the pathogenesis of AMD. ABCA1: adenosine triphosphate binding cassette A1; AMD: age-related macular degeneration; Ang: angiotensin; AT1R: angiotensin II type 1 receptors; BM: Bruch's membrane; ECM: extracellular matrix; ERK: extracellular signal-regulated kinase; H_2O_2: hydrogen peroxide; ICAM-1: intracellular adhesion molecule-1; MCP-1: monocyte chemoattractant protein-1; MMP: matrix metalloproteinases; NOX: nicotinamide adenine dinucleotide phosphate oxidase; $O_2^{\bullet-}$: superoxide anion radical; PRR: (pro)renin receptor; RPE: retinal pigment epithelium; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

for the prevention and management of patients with AMD.

The therapeutic potential of RAAS blockade in patients with AMD was also evaluated in a US population-based, cross-sectional study of 3023 hypertensive patients aged 40 years and older undergoing therapy with RAAS inhibitors. This multivariable logistic regression analysis revealed that RAAS inhibitors were not associated with direct effects on AMD prevalence. However, long-term treatment (> 5 years) had beneficial effects for early and late AMD, reducing the development of soft drusen and geographic atrophy [16]. Other studies found controversial results, with no evidence that the use of ACE inhibitors is protective against AMD in patients with arterial hypertension [330,331]. However, interventional studies elucidating the effects and safety of RAAS inhibition in AMD are lacking.

Fig. 10 summarizes the main events on the basis of the current literature upon the connection between ocular RAAS and occurrence and development of AMD.

3.5. Retinal vein occlusion

3.5.1. General aspects

Retinal vein occlusion (RVO) is a vascular disorder of the retina, affecting millions of individuals globally and recognized as the second most prevalent retinovascular disease after DR [332–334]. It results from thrombus formation and subsequent occlusion of retinal vessels—specifically the central retinal vein, hemi-central retinal vein, or a branch retinal vein, often due to progressive compression by adjacent arteries [335,336]. Aging, arterial hypertension, and vessel atherosclerosis are predominant risk factors for RVO [332,335]. Clinically, RVO is characterized by retinal edema, hemorrhages, and vascular tortuosity observable during fundus examination [337]. Despite advances in diagnostic tools and therapeutic interventions, there remains a significant unmet need for optimal RVO management. This has driven ongoing research into the disease's pathophysiology, aiming to identify novel pharmacological targets and develop innovative treatment approaches [338,339].

Pathogenetically, RVO is known to trigger severe ischemia–reperfusion (I/R) injury in the retina [340]. Remarkably, experimental models have shown that I/R injury upregulates components of the RAAS, including the AT1R [340]. In animal studies, RAAS modulator, such as ACE inhibitors, AT1R antagonists, and MR antagonists, have been shown to mitigate retinal I/R damage [340–342], suggesting a potential role of the RAAS in the pathogenesis of RVO-related ischemic injuries [343].

3.5.2. RAAS in retinal vein occlusion: risk factors and pharmacological targets

Interestingly, Kutluturk et al. identified the ACE D/D polymorphism as a possible independent predictive factor for RVO [344], although the evidence did not conclusively establish it as a definitive risk factor. In contrast, hypertension is a well-established risk factor for RVO [147, 345]. Of note, primary hyperaldosteronism, a condition of aldosterone excess, is present in approximately 5–15 % of hypertensive patients, and up to 20 % in those with resistant hypertension [346]. Given this association, Allingham and colleagues investigated the effects of systemic aldosterone administration in a murine model of RVO. Their findings revealed that aldosterone exacerbates retinal pathology, including increased edema, ischemia, and hemorrhage [347]. Moreover, aldosterone intensified Müller cell damage and impaired fluid regulation by disrupting the function of key fluid transport proteins, aquaporin-4 (AQP4) and inwardly rectifying potassium channel Kir4.1 [347].

In summary, existing literature supports a role for the RAAS, particularly aldosterone, in the pathophysiology of ischemic retinal injuries observed in RVO. RAAS activity appears to exacerbate ischemia-induced retinopathy, potentially through glial cell dysfunction and

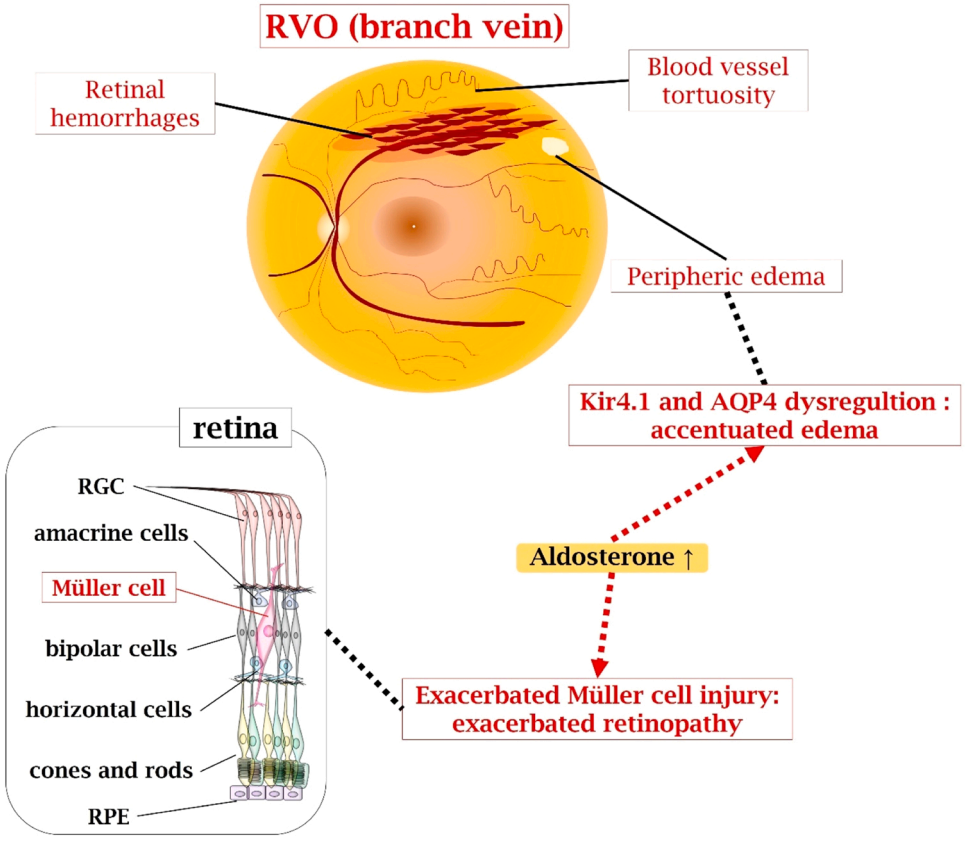

Fig. 11. Illustration of the proposed model elucidating the role of RAAS in RVO. AQP4: aquaporin 4; Kir: inward-rectifier potassium channel; RGC: retinal ganglion cell; RPE: retinal pigment epithelium; RVO: retinal vein occlusion.

fluid pump dysregulation. Nevertheless, further experimental studies are necessary to validate and expand upon these findings. Fig. 11 provides a schematic overview of the proposed involvement of RAAS in RVO.

3.6. Retinopathy of prematurity

3.6.1. Epidemiological aspects and clinical presentation

Retinopathy of prematurity (ROP) is a prevalent cause of childhood blindness in premature infants. Between 1985 and 2021, the pooled global prevalence of ROP was 31.9 %, with severe ROP occurring in 7.5 % of cases [348]. Among infants with a birth weight under 1251 g, the incidence of any ROP was 68 %, and severe ROP occurred in 36.9 % of these infants [349]. Birthweight and gestational age are the primary risk factors for ROP [314]. Premature children often require oxygen support after birth and are exposed to a hyperoxic environment. Under hyperoxia, the suppression of growth factors such as VEGF and insulin-like growth factor (IGF-1), along with hypoxia-inducible factors (HIFs) and erythropoietin, leads to disturbed retinal vessel growth and regression of already formed vessels. This occurs in a state of oxidative stress, attributed to mitochondrial dysfunction and NOX activity, ultimately contributing to endothelial cell apoptosis and vaso-obliteration [350]. In later stages of the disease, retinal ischemia establishes and triggers the release of growth factors, resulting in the formation of pathological neovascularization [351]. Advanced stages are characterized by the growth of these vessels into the vitreous, causing retinal detachment and consequent vison loss [314]. Treatment options depend on the disease stage and include laser photocoagulation, ablative cryotherapy, and intravitreal injection of anti-VEGF agents [352,353].

3.6.2. The RAAS in retinopathy of prematurity: involvement in oxidative stress and neovascularization

The release of vasoproliferative growth factors, such as VEGF, in response to oxygen-induced retinopathy is central to the pathogenesis of ROP. Under these conditions, the retinal vasculature is highly susceptible to pathological activation of the RAAS. Studies have shown that blocking RAAS components can mitigate angiogenesis, inflammation, and glial damage in animal models of ROP [354–356]. Sarlos et al. discovered that the developing rat retina contains all components of the RAAS, found in both blood vessels and in cells of the RGC layer. In rats overexpressing the RAAS, the growing vasculature extended farther into the retinal periphery, and vascular density was increased compared to controls, indicating a potential role of the RAAS in retinal vascularization [357]. Histological studies revealed increased endothelial cell numbers in one-week old mice exposed to hyperoxic conditions, followed by normoxia-induced relative hypoxia, compared to mice kept in room air. Treatment with the ACE inhibitor perindopril significantly decreased endothelial cell numbers, reduced penetrating capillaries, and minimized endothelial cell tuft size and number compared to vehicle-treated hypoxic pups [358]. Another ROP model indicated that AT1R blocker administration reduced the loss of amacrine cells, potentially preventing scotopic vision impairments and neuronal anomalies during ROP [359]. This study has suggested that an increased activation of the RAAS is present during ROP, and may promote disease progression. Likewise, in the vitreous humor of patients with ROP, a significant increase of RAAS components and angiogenic cytokines was found compared to respective age matched controls [23]. These findings were confirmed by experimental studies in rat pubs with oxygen induced retinopathy and pubs kept in normoxia. Multiple fold up-regulation of mRNA for RAAS components was detected in hyperoxic pups [23].

Remarkably, in the context of RAAS overactivation, Ang II and aldosterone dramatically impact the retina by triggering excessive ROS production, likely via NOX upregulation [360]. Studies have reported a substantial correlation between VEGF expression and ROS generation, both fundamentally relevant in ROP [361,362]. In a rodent model of retinal ischemia/reperfusion, candesartan was effective in mitigating the NOX-related ROS formation by modulating AT1R signaling during the ischemic insult [341]. In an ROP animal model, aldosterone infusions increased NOX4 mRNA levels, modulating oxidative stress, retinal inflammation, and leukocytosis, while aldosterone blockade with spironolactone reversed these effects [92].

Additionally, ACE inhibitors and AT1R blockers can significantly reduce VEGF levels, explaining a potential role of the RAAS in vasoproliferation during ROP. Moreover, electroretinographic analyses showed that functional retinal parameters could be restored by ACE inhibitors and AT1R blockers [23]. Intraperitoneal injection of enalaprilat decreased activity of RAAS at retinopathy onset in a ROP rat model, though potential drug toxicity necessitates further dosage and safety studies [24]. Oxygen-induced retinopathy is also characterized by pathological vessel growth into the vitreous in the peripheral retina, elevated microglial number and activation, and impaired rod and cone pathway function. Valsartan, an AT1R inhibitor, reduced both pathological vessel growth into the vitreous and physiological angiogenesis of the deep vascular plexus, while also reducing microglial number and activation. However, retinal function improvement did not occur, and high doses even decreased photoreceptor and inner retinal function [363]. These findings indicate that a precise adjustment of the dosage is required to achieve beneficial effects by RAAS inhibition.

Case reports of infants exposed to RAAS blockade during gestation, resulting in severe ROP development, highlight the problem that ACE inhibitors and AT1R blockers can affect both pathological and physiological vascularization of the retina and other organs [364]. Inhibition of aldosterone synthase, such as with the inhibitor FAD286, may offer an alternative approach. FAD286 reduced retinal neovascularization and tufts in rats with oxygen-induced retinopathy, normalizing VEGF mRNA and protein levels [296]. These findings suggest that inhibiting RAAS later in the signaling cascade achieves effects comparable to ACE or AT1R inhibition.

Additionally, high levels of prorenin in the retina and vitreous during ROP, along with (P)RR localization in the retina, suggest that suppressing (P)RR may benefit the ROP-afflicted retina [3,365,366]. However, inhibiting (P)RR has been shown to decrease retinal neovascularization during ROP, but with deleterious effects on retinal neurons and glia, as indicated by electroretinogram studies [367].

Further studies are needed to elucidate the protective effects and challenges of RAAS inhibition in ROP. However, conducting clinical studies in this vulnerable population presents considerable ethical and practical challenges. Designing trials involving premature infants is particularly complex due to the delicate balance between potential therapeutic benefits and the risks posed to developing organ systems. Notably, fetotoxic effects, such as renal tubular dysgenesis and pulmonary hypoplasia, have been linked to the use of ACE inhibitors and AT1R blockers during pregnancy. As a result, administering these agents to premature infants, whose organs are not yet fully developed, could significantly increase the risk of congenital abnormalities or organ dysfunction [368]. At present, the safety of RAAS inhibitors in this patient population remains a subject of debate, with conflicting evidence that necessitates careful evaluation in future studies [369]. Fig. 12 summarizes the main pathomechanisms leading to ROP, highlighting the proposed role of the RAAS in oxidative stress and illustrating how RAAS modulators counteract ROP by antagonizing angiogenic events.

3.7. Central serous chorioretinopathy

3.7.1. General characteristics

Central serous chorioretinopathy (CSCR), first described by Albrecht von Graefe in 1866 as a ‘relapsing central luetic retinitis’, is a common chorioretinal disease. It is primarily characterized by retinal neurosensory and pigment epithelial detachments and processes of choroidal thickening [370,371]. Initial symptoms include central vision loss, image distortion, and loss of color and contrast vision. These symptoms typically occur in individuals aged 20–50, predominantly affecting

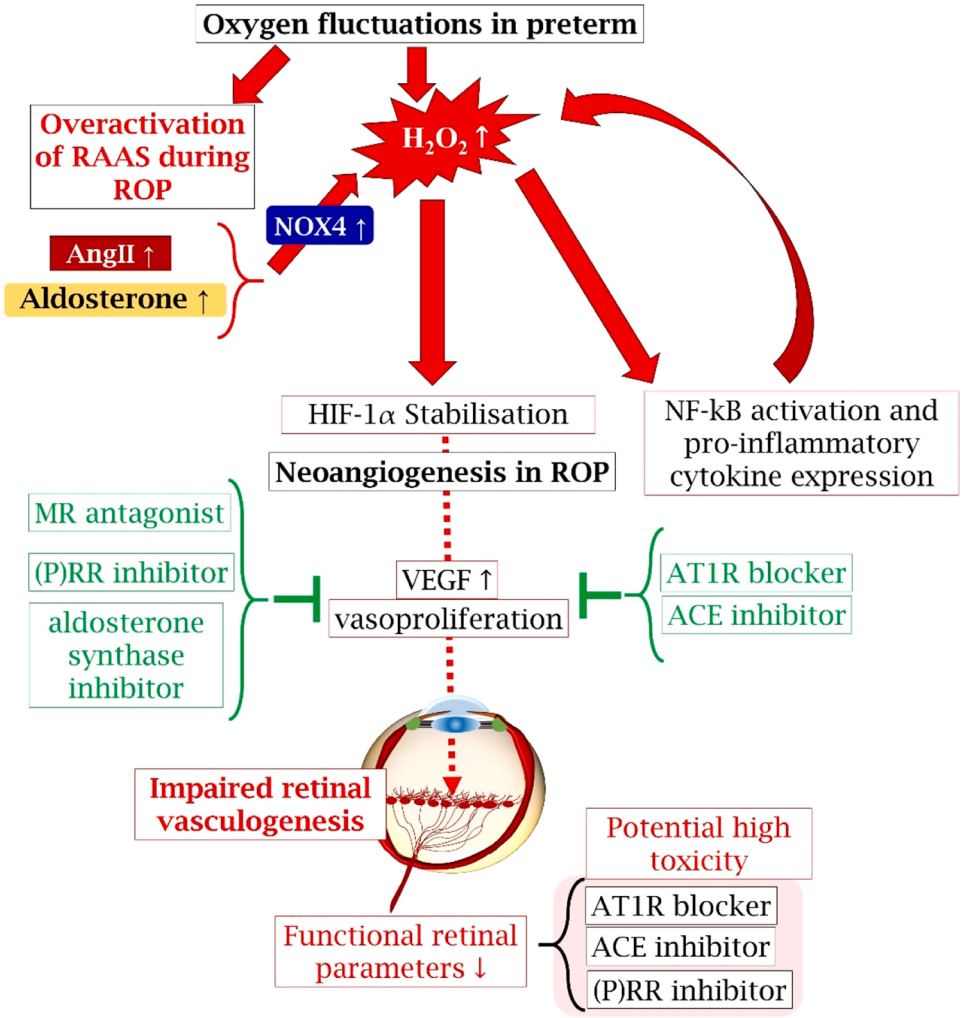

Fig. 12. Schematic overview of the pathomechanisms in ROP, its link with oxidative stress and RAAS activation, and the mechanistic activities of RAAS modulators to counteract the progression of ROP. ACE: angiotensin-converting enzyme; Ang: angiotensin; AT1R: angiotensin II type 1 receptors; H_2O_2: hydrogen peroxide; HIF-1α: hypoxia inducible factor 1α; MR: mineralocorticoid receptor; NF-kB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NOX: nicotinamide adenine dinucleotide phosphate oxidase; PRR: (pro)renin receptor; RAAS: renin-angiotensin-aldosterone system; ROP: retinopathy of prematurity; VEGF: vascular endothelial growth factor.

males, making CSCR a significant vision-threatening condition in middle-aged individuals [372–375]. Most cases present acutely and generally remit spontaneously within a few months. However, chronic and unresolved CSCR can lead to choroidal neovascularization, cystoid macular degeneration, and foveal atrophy, potentially resulting in vision loss [376–381]. The pathophysiology of CSCR is is complex, with various endocrine agents influencing disease onset [382]. However, glucocorticoids and mineralocorticoids, such as aldosterone, are particularly relevant [383]. CSCR is often diagnosed in patients exposed to systemic glucocorticoid drugs or during periods of stress, which increase endogenous glucocorticoid activity [374]. Consistent with this observation, endogenous hypercortisolism has also been associated with CSCR [384]. Given that the mineralocorticoid receptor binds both aldosterone and glucocorticoids, over-activation of this receptor may lead to CSCR [385,386].

3.7.2. Aldosterone and central serous chorioretinopathy: mechanisms and controversies

Activation of the mineralocorticoid pathway in vascular tissues promotes vasoconstriction, inflammation, aberrant vascular remodeling, and fibrosis [387]. Hyperstimulation of aldosterone has been implicated in the pathophysiology of CSCR [388–390]. A preclinical study in rats has shown that mineralocorticoid administration induced choroidal changes similar to those observed in CSCR patients [145]. Another recent study in rodents showed that chronic aldosterone exposure upregulated genes associated with inflammation, such as *IL-1*, *IL-6* and components of the NF-κB and TNF-α pathways, as well as genes linked to oxidative stress, synapse formation, and muscle contraction in the RPE-choroid complex. These molecular changes led to retinal edema, RPE phagocytosis dysfunction, and choroidal vasodilation [391]. Choroidal vasodilation, a hallmark of CSCR, may result from aldosterone-mediated downregulation of ion pump-regulating genes that influence the electrical activity of nerve and muscle cells. Furthermore, aldosterone suppressed the expression of genes critical for smooth muscle contractility, including *Mylk, Calm2, Acta2, Myh11*, thereby contributing to the dilation of choroidal vessels [392]. These findings may explain CSCR in patients with primary hyperaldosteronism, where chronic aldosterone overstimulation affects the choroidal vasculature and promotes endothelial dysfunction, oxidative stress, hypertrophic remodeling, and fibrosis [393].

Aldosterone modulates fluid homeostasis in the retina by regulating the expression of various ion channels, including ENAC-α, Kir4.1, AQP4 and KCa2.3 [144,145]. It also drives inflammation by stimulating NF-kB and major inflammatory mediators like TNF-α and IL-1β and promotes

angiogenesis via the SDF-1/Cxcr4 axis, which facilitates RPE cell migration, blood-retinal barrier disruption, and neovascularization [146,391,394–398]. Additionally, aldosterone triggers upregulation of NOX2 and NOX4, inducing ROS overproduction and oxidative stress [93,94]. High systemic oxidative stress levels have been found in CSCR patients, and MDA, a marker of lipid peroxidation, correlates with RPE leakage in CSCR [399–401]. Current literature indicates that a mineralocorticoid receptor over-activation in vascular endothelium triggers choroidal and RPE changes, leading to subretinal fluid accumulation and a clinical picture similar to CSCR [386].

Although aldosterone plays a significant role in CSCR, there is no FDA-approved treatment for the condition. Systemic mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, are used off-label with varying success [386]. However, several studies have linked high aldosterone levels to persistent CSCR, characterized by increased subfoveal choroidal thickness, suggesting the potential use of mineralocorticoid antagonists to treat the disorder [402–404]. Conversely, recent clinical trials, such as the VICI trial, have shown that eplerenone lacks effectiveness in treating chronic CSCR [405,406]. In another clinical study, Short-term eplerenone therapy reduced choroidal and central macular thickness but failed to decrease subretinal fluid height or significantly improve visual acuity [407]. Despite the limited benefits reported, eplerenone continues to be used in clinical practice, as evidenced by real-world experience [408]. Additionally, no studies to date have investigated the effects of RAAS inhibitors acting earlier in the cascade, such as ACE inhibitors or AT1R blockers, on CSCR, highlighting a promising avenue for future research.

In summary, the use of mineralocorticoid receptor antagonists in CSCR remains debated. While some trials have shown a lack of effectiveness, other studies highlight their persistent use in clinical practice. There is an opportunity to test new formulation methods in nano-therapeutic systems to achieve maximum efficiency for ocular delivery in CSCR [409].

Fig. 13 summarizes the main mechanistic pathways triggered by the binding of aldosterone with mineralocorticoid receptor during CSCR in RPE cells.

3.8. Epiretinal membrane

3.8.1. General characteristics

Epiretinal membrane (ERM) is a common vitreoretinal disorder, with a reported prevalence ranging from 7 % to 11 %, and aging identified as the most significant risk factor [410–412]. ERM is classified as either primary (idiopathic) or secondary, with the latter associated with conditions such as ocular trauma, intraocular tumors, cataract surgery, retinal vascular diseases, and uveitis [413,414]. The idiopathic form is the most prevalent, although only a minority of cases become symptomatic. As a result, surgical intervention is required in a relatively small proportion of patients [412].

Pathogenetically, ERMs are characterized by aberrant fibrocellular proliferation at the vitreoretinal interface, specifically over the internal limiting membrane [410,411]. Disease progression is marked by an increase in myofibroblast-like cells and ECM deposition, contributing to membrane contraction and subsequent retinal distortion or traction [415,416]. Fibrogenic processes play a central role in ERM pathophysiology, with the TGF-β1 signaling pathway being a key driver of myofibroblastic transdifferentiation and fibrosis [417]. In this context, it is noteworthy that RAAS modulators, such as AT1R antagonists and ACE inhibitors, have demonstrated anti-fibrotic effects by inhibiting TGF-β1 signaling, suggesting a potential therapeutic avenue for targeting

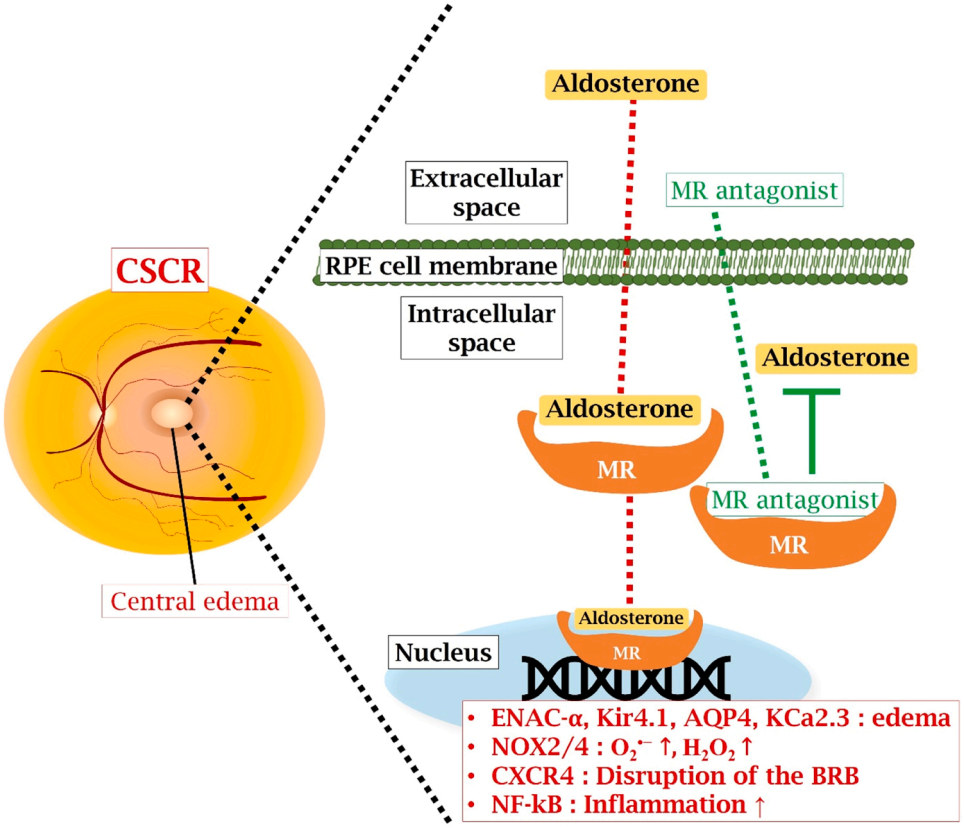

Fig. 13. Schematic illustration of the action performed by aldosterone binding MR during CSCR in RPE cells. AQP4: aquaporin 4; BRB: blood-retinal barrier; CSCR: central serous chorioretinopathy; CXCR4: chemokine receptor type 4; ENAC-α: epithelial sodium channel subunit α; H_2O_2: hydrogen peroxide; Kir: inward-rectifier potassium channel; KCa: calcium-activated potassium channel; MR: mineralocorticoid receptor; NF-kB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NOX: nicotinamide adenine dinucleotide phosphate oxidase; $O_2^{\bullet-}$: superoxide anion radical.

fibrosis in ERM [418–421].

3.8.2. RAAS in epiretinal membranes: modulating fibrosis with RAAS inhibitors

Given the central role of fibrogenesis in ERM pathophysiology and the relevance of RAAS in modulating fibrotic processes, Dong and colleagues investigated the effects of prorenin and Ang II on Müller cells isolated from idiopathic ERM tissues [139]. The authors demonstrated that prorenin increased the expression of fibroblast growth factor 2 (FGF2), while Ang II elevated the expression of glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and TGF-β1. Additionally, an upregulation of the (pro)renin receptor [(P)RR] and AT1R was observed in glial cells from ERM samples. Notably, the effects of prorenin and Ang II were reversed by the use of specific (P)RR and AT1R blockers, respectively [139].

More recently, Confalonieri and colleagues reviewed the existing literature on the potential link between RAAS modulators, such as AT1R blockers and ACE inhibitors, and the spontaneous resolution of ERM [422]. Their analysis highlighted clinical evidence suggesting a possible association between the use of AT1R blockers and ERM regression. They hypothesized that the anti-fibrotic effects of RAAS modulators might be mediated through inhibition of the TGF-β signaling pathway [422]. The authors further proposed a molecular mechanism by which AT1R blockers may reduce fibrogenesis in ERM by modulating the JAK/STAT and MAPK signaling pathways, leading to decreased expression of fibronectin, collagen, and TGF-β [419,423,424].

Further studies are warranted to validate and better understand the potential therapeutic benefits of AT1R antagonists and ACE inhibitors in the management of ERM.

Fig. 14 proposes a model elucidating the role of RAAS in ERM.

3.9. Uveitis

3.9.1. General aspects

Uveitis is a sight-threatening intraocular inflammatory disease that can involve different tissues within the eye. It is anatomically classified into anterior, intermediate, posterior, or panuveitis, depending on the affected ocular structure [425]. Additionally, uveitis can be categorized based on its histopathological profile as granulomatous or non-granulomatous, and by the type of inflammation as acute, chronic, or recurrent [426]. In terms of etiology, uveitis is divided into infectious and non-infectious forms [427,428].

Globally, uveitis is one of the major causes of severe visual impairment among the working population [429]. Established treatments for managing uveitis include corticosteroids, immunosuppressive agents, and biological therapies [430,431]. However, the significant long-term side effects of these drugs, along with limited responsiveness, compliance, and tolerance in patients, underscore the need for developing novel, effective therapeutic approaches [432–434].

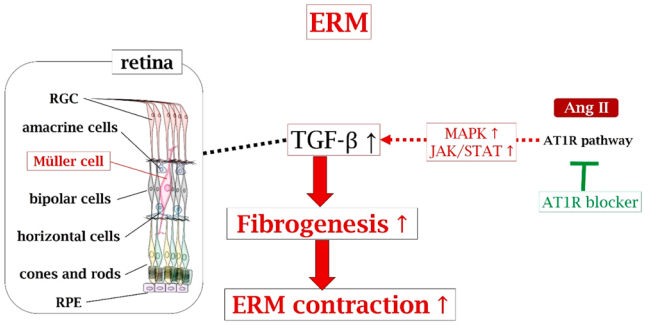

Fig. 14. Proposed model representing the role of RAAS in ERM. Ang: angiotensin II; AT1R: angiotensin II receptor type 1; ERM: epiretinal membrane; JAK: janus kinase; MAPK: mitogen-activated protein kinase; STAT: signal transducer and activator of transcription; RGC: retinal ganglion cell; RPE: retinal pigment epithelium; RVO: retinal vein occlusion; TGF-β: transforming growth factor β.

3.9.2. The RAAS in uveitis: contribution to the inflammatory state

Inflammatory mediators such as TNF-α and NF-kB, triggered by infections, autoimmune reactions, or excessive ROS, are involved in the pathogenesis of uveitis [435–439]. In an animal model of autoimmune uveitis, Nguyen and Rao reported that the innate immune response in photoreceptors is initiated via TLR4 activation, leading to the overexpression of pro-inflammatory cytokines, disruption of redox homeostasis, and mitochondrial DNA damage, exacerbating oxidative stress [440]. Consequently, emerging experimental therapies include antioxidants such as curcumin, resveratrol, and N-acetylcysteine [441–443]. Interestingly, Investigations have found elevated serum levels of RAAS components, particularly ACE, in patients with uveitis, highlighting RAAS overactivation in this condition as in other ocular disorders [444–446]. These studies have substantially indicated that also in uveitis, as in other several ocular disorders, the RAAS is overactivated. Given the pro-inflammatory and pro-oxidative nature of RAAS, several studies have explored modulating RAAS to antagonize inflammation and counteract uveitis progression in both murine models of endotoxin-induced uveitis (EIU) and experimental autoimmune uveoretinitis (EAU) For example, Nagai and colleagues found that suppressing AT1-R signaling with Telmisartan in an animal model of EIU blocked retinal ICAM-1 upregulation and leukocyte adhesion and infiltration during uveitis [447]. Similarly, another study demonstrated that intravenous administration of losartan in an EIU model downregulated NF-kB in the iris and ciliary body and decreased TNF-α and MCP-1 levels in the aqueous humor, indicating the effectiveness of AT1R inhibitors in counteracting acute ocular inflammation [27]. Additionally, levels of prorenin and the (P)RR have been shown to be elevated in uveitis. Satofuka and co-workers demonstrated that inhibiting (P)RR signaling using a decoy handle-region peptide in a rodent model of EIU effectively blocked leukocyte adhesion and infiltration and reduced ICAM-1, CCL2/MCP-1, and IL-6 expression [448]. Similarly, Okunuki et al. found that telmisartan suppressed ICAM-1 and MCP-1 expression, leukocyte retinal adherence, and antigen-specific T-cell activation in an EAU model [449]. Ilieva and associates showed that captopril, an ACE inhibitor, suppressed NF-kB signaling and reduced levels of pro-inflammatory cytokines such as TNF-α and MCP-1, NO, and PGE2 in a rodent EIU model [450].

Interestingly, a study showed that short-term aldosterone administration in an EIU rodent model could decrease inflammation in the iris and ciliary body by inhibiting pro-inflammatory cytokine production and reducing the number of activated microglia/macrophages. This suggests that the mineralocorticoid receptor pathway activation may protect against uveitis-related damage, potentially by preventing uveitis-induced mineralocorticoid receptor downregulation and rebalancing the its activation with the glucocorticoid receptor pathway [451]. Other studies have confirmed that aldosterone can decrease LPS-induced microglial activation by reducing MAPK and NF-kB activation [452]. However, the molecular mechanisms of aldosterone's effects in uveitis remain unclear, requiring further research

Other research has also focused on activating the counter-regulatory arm of RAAS, such as the ACE2/Ang (1–7)/MasR axis, to manage uveitis. In this context, Shil and colleagues reported that oral delivery of bioencapsulated ACE2/Ang (1–7) in an EIU model suppressed inflammatory cell infiltration and the expression of IL-1β, IL-6, TNF-α, ICAM-1, and MCP-1. In an EAU model, this approach significantly mitigated inflammation and improved histological findings [453]. Another study showed that local and systemic administration of the ACE2 activator diminazene aceturate reduced inflammatory cell infiltration and pro-inflammatory cytokine expression in an EIU model [26]. In an EAU mouse model, subretinal delivery of ACE2 gene via an adenoviral vector inhibited inflammation by suppressing MAPK, NF-κB, and STAT3 signaling pathways [454].

Despite the promising preclinical findings on inhibiting AT1R signaling and the ACE pathway or activating the ACE2/Ang (1–7)/MasR axis, clinical trials have failed to demonstrate significant improvements in managing uveitis or inflammatory cystoid macular edema with ACE inhibitors [455,456].

Fig. 15 summarizes the mechanistic pathways triggered by RAAS overactivation that lead to inflammation and edema in uveitis and illustrates the action of RAAS modulators in counteracting uveitic processes.

4. Points of question and future challenges

The ocular RAAS, functioning independently from the circulatory system, presents a potential target for RAAS modulators to treat ocular disorders. However, the clinical effectiveness of these drugs in ophthalmology remains uncertain [457]. Despite several preclinical and experimental studies highlighting the pathophysiological significance of RAAS in the eye and the potential benefits of RAAS modulators for specific ocular pathologies, recent years have seen increasing controversies regarding their use to improve patient outcomes. The complexity of the RAAS, its varied effects on different ocular tissues, and its overactivation associated with oxidative stress, inflammation, and neovascularization, create a challenging pathogenetic scenario to decipher [8]. Our understanding of the ocular RAAS in conditions such as CSCR and uveitis is still limited. The use of RAAS inhibitors remains questionable and requires continuous monitoring and validation [386].

According to our data, key questions include the modulation of the mineralocorticoid receptor pathway and the role of aldosterone. Notably, the therapeutic targeting of the mineralocorticoid receptor in CSCR has been completely overturned in recent years, with current international guidelines no longer recommending the use of eplerenone [386,405,406]. Additionally, while a mineralocorticoid receptor antagonism appears beneficial in DR, ROP, and AMD [20,92,146], the administration of aldosterone in uveitis and LPS-activated microglia has shown positive effects against disease progression [451,452].

Another important area needing further exploration is the modulation of AT2R signaling. Although studies have described anti-fibrotic, antioxidant, and vasorelaxant effects through AT2R activation [14,96–98], AT2R antagonism has been reported to suppress neoangiogenic pathways and upregulate VEGF in DR [99].

Given the significant role of the RAAS in the pathogenesis of numerous ocular diseases, the development of innovative therapies that modulate RAAS activity represents a promising frontier for future research. Traditional RAAS modulators, such as ACE inhibitors and AT1R blockers, have shown beneficial effects in certain ocular conditions. Consequently, novel therapeutic approaches are being explored.

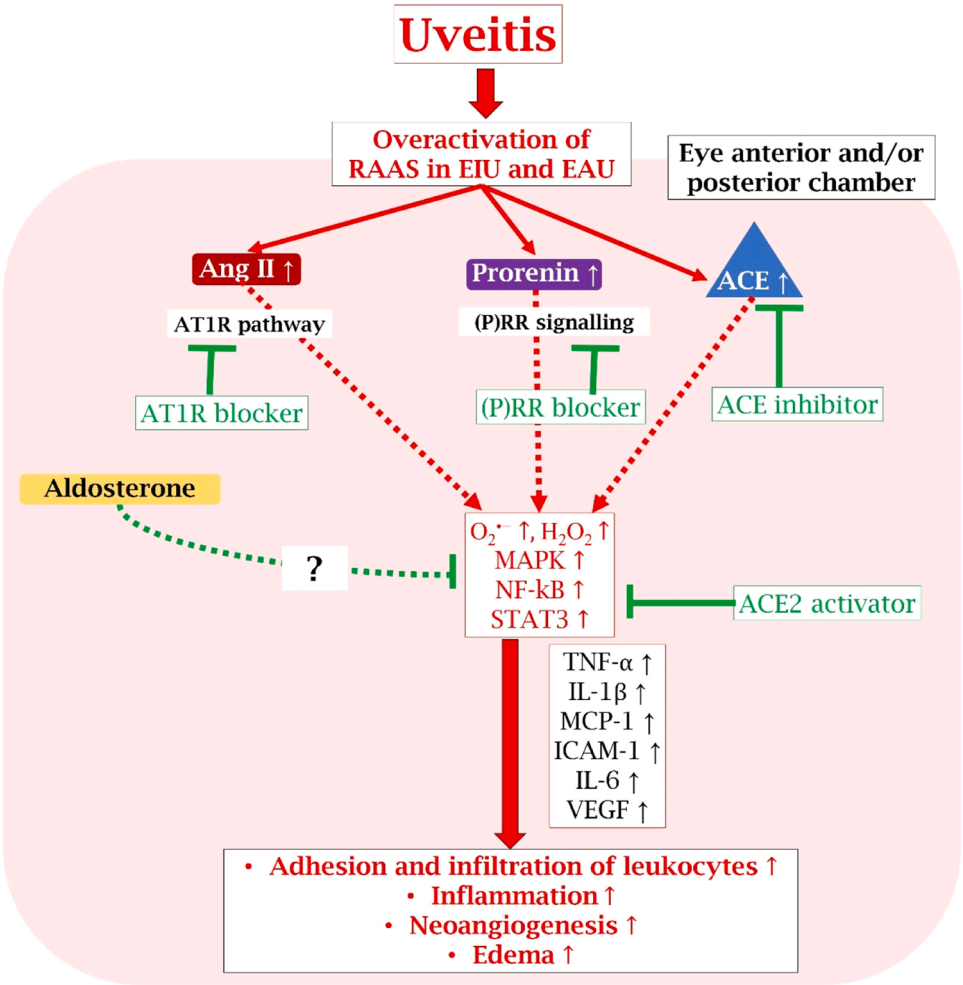

Fig. 15. Overview on the involvement of RAAS in the pathophysiology of uveitic processes. ACE: angiotensin-converting enzyme; AT1R: angiotensin II type 1 receptors; EAU: experimental autoimmune uveoretinitis; EIU: endotoxin-induced uveitis; H_2O_2: hydrogen peroxide; ICAM-1: intercellular adhesion molecule 1; IL-1β: interleukin 1β; IL-6: interleukin 6; MAPK: mitogen activated protein kinase; MCP-1: monocyte chemoattractant protein 1; MR: mineralocorticoid receptor; NF-κB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; $O_2^{\bullet-}$: superoxide anion radical; PRR: (pro)renin receptor; STAT3: signal transducer and activator of transcription 3; TNF-α: tumor necrosis factor α; VEGF: vascular endothelial growth factor.

Localized drug delivery methods, including topical eye drops and intraocular injections, aim to administer ACE inhibitors or AT1R blockers directly to the anterior or posterior segments of the eye. This targeted approach enhances ocular drug concentration while minimizing systemic side effects. Simultaneously, the identification of new molecular targets within the RAAS cascade is expanding therapeutic possibilities. Notable examples include (P)RR blockers and ACE2 activators [126,458–460], as well as renin inhibitors such as aliskiren, Ang (1–7), and MasR agonists [461]. These advances reflect a broader shift toward precision-targeted RAAS modulation, which may ultimately transform the management of ocular diseases. Nevertheless, this research area remains relatively nascent in ophthalmology, requiring careful validation through robust preclinical and clinical studies.

One particularly promising avenue is multi-target combination therapy. For instance, co-administration of losartan and aliskiren has been shown to reduce pathological remodeling of the retinal microvasculature [462]. Moreover, cutting-edge technologies, such as metabolomics and gene sequencing, offer the potential to uncover RAAS-driven metabolic alterations, identify novel biomarkers, and map retinal cell populations with elevated expression of AT1R or ACE2. These insights could help decode the complex signaling dynamics of RAAS in the ocular microenvironment and support the stratification of disease subtypes, guiding the development of more personalized therapies.

Current progress in RAAS research has primarily been achieved through cellular and animal models, which have elucidated key mechanisms of RAAS signaling in ocular pathologies. Encouraging results from these studies suggest that RAAS-targeted therapies may hold substantial promise. However, continuous monitoring is essential, as illustrated by the mixed outcomes seen with mineralocorticoid receptor antagonists in CSCR.

Further studies are needed to evaluate the therapeutic potential of both RAAS activators and established inhibitors, particularly in human subjects. However, translating basic research into clinical practice will require robust clinical trials, clearly defined patient selection criteria, and a thorough evaluation of healthcare system implications. This includes considerations of cost-effectiveness, implementation feasibility, and long-term outcomes.

The clinical implications of RAAS-targeted therapies are expected to vary by ocular disease type. In glaucoma, therapeutic focus may center on evaluating RAAS component levels in AH and local inflammatory markers. For DR and uveitis, RAAS-related biomarkers in plasma or vitreous samples could inform clinicians early and guide decisions around preventive RAAS inhibition. Patient stratification prior to treatment initiation is essential, taking into account disease subtype and severity, potential adverse effects (e.g., hypotension, renal dysfunction, or electrolyte imbalance), and the presence of systemic comorbidities. Abnormalities in biomarkers like AT1R, MasR, and (P)RR suggest that disease progression may be closely linked to RAAS overactivation, indicating a higher likelihood of therapeutic response to RAAS inhibition. For patients already receiving therapies, such as anti-VEGF agents, steroids, or immunomodulators, the potential benefits and risks of combining RAAS-targeted drugs with existing treatments must be carefully weighed. Additionally, cost-effectiveness analyses should compare the long-term benefits of RAAS-targeted therapies against conventional treatments (e.g., anti-VEGF injections, steroids, other immunosuppressants), factoring in cost savings from reduced complications and balancing initial investments with long-term outcomes to improve cost-efficiency.

By proposing these clinical practice recommendations, we aim to support clinicians in effectively implementing RAAS-targeted treatments, while offering healthcare institutions strategic insights for optimizing resource allocation. As RAAS-based therapies are integrated into standard ophthalmic care, they hold the potential to significantly improve patient outcomes and enhance quality of life across a range of ocular diseases.

5. Concluding remarks

Pharmacological inhibition of the RAAS has historically been crucial for managing cardiovascular and renal disorders. The circulatory RAAS is recognized as a vital regulator of blood pressure and electrolyte balance. The ocular RAAS, functioning as an independent entity, offers potential targets for treating eye disorders. However, the suitability of these treatments for ocular applications is yet to be fully demonstrated. The interplay between overactivation of the ocular RAAS, oxidative stress, inflammation, and neovascularization varies across different disorders in the anterior and posterior eye segments.

This study provides a comprehensive and updated overview of the role of the RAAS in ocular diseases, highlighting its interconnection with oxidative stress. We have examined the central molecular signaling pathways triggered by the RAAS, reported on the beneficial effects of RAAS modulators found in preclinical studies, and individually reviewed widespread and severe eye diseases. Additionally, we have gathered data on novel drugs such as (P)RR blockers, Ang (1–7), and ACE2 activators, which activate the counter-regulatory arm of the RAAS. Conversely, we have identified limitations and challenges regarding the use of RAAS modulators in ophthalmology that require further research.

These intriguing observations could stimulate future studies to address key questions and develop new treatment approaches. This area of research holds great promise for combating ocular disorders and supporting the management of highly prevalent and vision-threatening conditions.

CRediT authorship contribution statement

Buonfiglio Francesco: Writing – original draft, Visualization, Conceptualization. **Böhm Elsa Wilma:** Writing – original draft. **Tang Qi:** Writing – original draft. **Gericke Adrian:** Writing – review & editing, Supervision, Conceptualization. **Daiber Andreas:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this papers.

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Data availability

No data was used for the research described in the article.

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