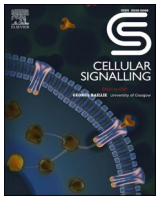
Cellular Signalling 122 (2024) 111343

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig



Glaucoma and the ocular renin-angiotensin-aldosterone system: Update on molecular signalling and treatment perspectives

Francesco Buonfiglio, Norbert Pfeiffer, Adrian Gericke *

Departments of Ophthalmology, University Medical Center of the Johannes Gutenberg- University, Langenbeckstr.1, 55131 Mainz, Germany

ARTICLE INFO

Keywords:
Glaucoma
Renin-angiotensin-aldosterone system
Pathophysiology
Molecular pathway
Oxidative stress
Inflammation
Remodelling
Treatment approach

ABSTRACT

Glaucoma, a leading cause of blindness worldwide, encompasses a group of pathological conditions affecting the optic nerve and is characterized by progressive retinal ganglion cell loss, cupping of the optic nerve head, and distinct visual field defects. While elevated intraocular pressure (IOP) is the main risk factor for glaucoma, many patients do not have elevated IOP. Consequently, other risk factors, such as ocular blood flow abnormalities and immunological factors, have been implicated in its pathophysiology. Traditional therapeutic strategies primarily aim to reduce IOP, but there is growing interest in developing novel treatment approaches to improve disease management and reduce the high rates of severe visual impairment. In this context, targeting the ocular renin-angiotensin-aldosterone system (RAAS) has been found as a potential curative strategy. The RAAS contributes to glaucoma development through key effectors such as prorenin, angiotensin II, and aldosterone. Recent evidence has highlighted the potential of using RAAS modulators to combat glaucoma, yielding encouraging results. Our study aims to explore the molecular pathways linking the ocular RAAS and glaucoma, summarizing recent advances that elucidate the role of the RAAS in triggering oxidative stress, inflammation, and remodelling in the pathogenesis of glaucoma. Additionally, we will present emerging therapeutic approaches that utilize RAAS modulators and antioxidants to slow the progression of glaucoma.

1. Introduction

Glaucoma is a major cause of irreversible visual loss worldwide [1–4], and elevated intraocular pressure (IOP) is recognized as the most significant risk factor for this disease [5,6]. Epidemiological studies reported that in 2013, approximately 64.3 million people aged 40 to 80 were affected by glaucoma, and by 2040, this number is projected to exceed 110 million [3]. Glaucoma encompasses progressive neurodegenerative disorders affecting the optic nerve, which, if left untreated, can lead to irreversible visual loss. Approximately 15–20% of patients may experience unilateral blindness, indicating a substantial economic burden on individuals and public health [7–10]. Currently, significant research efforts are directed towards developing more effective and innovative treatment strategies [11]. In this context, drugs targeting the renin-angiotensin-aldosterone system (RAAS) may be relevant as innovative medications. The RAAS, one of the most well-known hormonal networks, is recognized as a crucial physiological regulator of body fluid homeostasis and has been identified in its main components within various ocular structures, such as the retina, ciliary body, and choroid [12–14]. Chronic overactivation of the RAAS leads to several pathogenic effects, including endothelial dysfunction, chronic inflammation, neovascularization, and oxidative stress [15–25]. Current literature emphasizes the role of RAAS in the pathophysiology of many ocular disorders, including glaucoma [26–41], and various studies have highlighted the potential of targeting RAAS components to prevent the progression of glaucoma [30,42–44].

Within this background, our work aims to summarize the latest advancements in understanding the ocular RAAS, specifically focusing on involved intracellular cascades and their connection to inflammation and oxidative stress during glaucoma. Furthermore, we report on promising therapeutic approaches targeting RAAS, aiming to prevent glaucomatous damage.

2. General insights into glaucoma

2.1. Classification of glaucoma and risk factors

Glaucoma encompasses a spectrum of disorders characterized by the

* Corresponding author at: University Medical Center of the Johannes Gutenberg-University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany.
E-mail addresses: fbuonfig@uni-mainz.de (F. Buonfiglio), norbert.pfeiffer@unimedizin-mainz.de (N. Pfeiffer), adrian.gericke@unimedizin-mainz.de (A. Gericke).

https://doi.org/10.1016/j.cellsig.2024.111343
Received 30 June 2024; Received in revised form 29 July 2024; Accepted 8 August 2024
Available online 8 August 2024

progressive death of retinal ganglion cells, optic disc cupping, and distinct visual field defects [45]. It is one of the leading causes of irreversible visual loss worldwide, with elevated intraocular pressure (IOP) being the most significant risk factor [1–6]. Glaucomatous conditions are categorized into primary forms, where no associated ocular disease is present, and secondary forms, where coexisting pathological processes, such as uveitis and neovascularization, trigger IOP elevation and retinal ganglion cell loss [46–48]. Both primary and secondary forms are further classified into open-angle glaucoma and angle-closure glaucoma, referring to the angle between the iris and cornea in the anterior chamber [47,49,50]. Primary open-angle glaucoma (POAG), the most prevalent form worldwide, is often associated with raised IOP and evolves silently and chronically. In contrast, primary angle-closure glaucoma presents more rapidly and is considered an ocular emergency requiring immediate intervention [3,48,51]. In POAG, IOP elevation is primarily attributed to increased outflow resistance of aqueous humor, potentially due to remodelling processes in the trabecular meshwork (TM), a critical structure at the chamber angle. The increased resistance of aqueous humor outflow leads to the collapse of Schlemm's canal and compression of the TM, creating a positive feedback loop that further elevates IOP [52,53]. Inflammation, oxidative stress, fibrogenesis, and remodelling in the TM are fundamental pathogenetic drivers that induce increased resistance to aqueous humor turnover [54–56]. Importantly, POAG also includes a subtype known as normal-tension glaucoma (NTG), where IOP is not elevated. This suggests the relevance of alternative pathogenetic drivers, such as systemic arterial hypotension, orthostatic hypotension, abnormal autoregulation, endothelial dysfunction, and immunological aspects in its pathogenesis [57–68].

2.2. *Established pharmacological strategies to manage glaucoma*

The progression of POAG is generally asymptomatic due to binocular compensation, with affected individuals often experiencing the first symptoms only in the advanced stages of the disease [51,69]. Therefore, diagnostic tools such as tonometry, fundoscopy, and perimetry are critical for early detection and preventing disease progression [51,70,71]. From a therapeutic perspective, the primary goal of established antiglaucoma drugs is to decrease IOP to an acceptable range for the individual, thereby preventing the progression of glaucoma [72]. Medications that reduce elevated IOP do so by either diminishing aqueous humor production or increasing trabecular and uveoscleral drainage routes. For example, prostaglandin analogues like latanoprost enhance uveoscleral and trabecular outflow, while β-blockers such as timolol, α2-adrenoceptor agonists like brimonidine, and carbonic anhydrase inhibitors (e.g., brinzolamide) decrease aqueous humor production [51]. Additionally, α_2- adrenoceptor agonists can also increase trabecular outflow, similar to prostaglandins [51]. Miotic agents, such as pilocarpine, widen the chamber angle and provide a neuroprotective effect by activating muscarinic receptors [73]. A new class of antiglaucoma drugs, Rho-associated protein kinase inhibitors, such as netarsudil, approved in 2017, works by inhibiting the Rho-kinase and the norepinephrine transporter to increase aqueous humor outflow through the TM, thereby reducing IOP [74,75]. Although targeting IOP remains the most effective and widely used treatment strategy for glaucoma [76], recent research has highlighted the role of neuroinflammation and disrupted redox homeostasis in glaucoma. This suggests the potential for new treatment strategies targeting immune signalling pathways and counteracting reactive oxygen species (ROS) generation [11,77]. In this context, an intriguing and innovative area of research for antiglaucoma drugs involves RAAS modulators, considering the significant role of the ocular RAAS in the pathogenesis of glaucoma. Fig. 1 provides a schematic overview of the eye, particularly focusing on the anterior chamber and on the mechanisms of action of the main antiglaucoma drugs on critical structure for the regulation of IOP, such as the TM and the ciliary body.

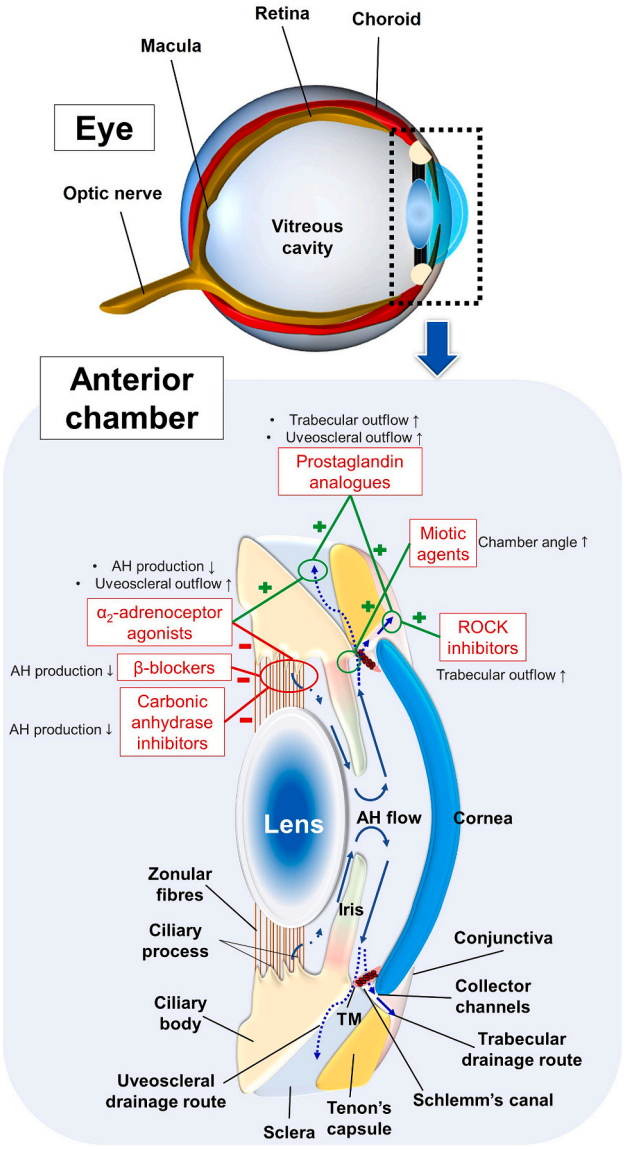


Fig. 1. Schematic representation of the eye and in particular of the anterior eye segment, with focus on the ocular structures responsible to modulate intraocular pressure, and on the mechanisms of action of established antiglaucoma drugs. AH: aqueous humor (clear fluid that fills the anterior chamber between the cornea and the lens); anterior chamber (space between the cornea and the iris, filled with aqueous humor); choroid (vascular layer between the retina and the sclera that supplies nutrients and oxygen to the retina); ciliary body (structure that produces aqueous humor and contains the ciliary muscle, which controls the shape of the lens); ciliary process (structure producing aqueous humor); conjunctiva (transparent membrane that covers the sclera and the inside of the eyelids); collector channels (part of the aqueous humor drainage system); cornea (transparent, dome-shaped surface that covers the front of the eye); macula (small, central area of the retina responsible for detailed vision); optic nerve (nerve that transmits visual information from the retina to the brain); retina (thin layer of tissue at the back of the eye that contains photoreceptor cells and converts light into neural signals); ROCK: Rho-associated protein kinase inhibitors; Schlemm's canal (circular channel located at the angle of the anterior chamber, which collects aqueous humor from the trabecular meshwork); sclera (white, outer layer of the eye that provides protection and structure); Tenon's capsule (fascial sheath of the eyeball); TM: trabecular meshwork (mesh-like structure at the angle where the iris meets the cornea that facilitates the outflow of aqueous humor); zonular fibres (also zonule of Zinn, ring of fibrous strands forming a little band that connects the ciliary body with the crystalline lens).

3. Classical and ocular RAAS

3.1. Insights into the classical RAAS

The classical RAAS is an essential endocrine system that regulates blood pressure (BP), fluid volume, and electrolyte balance, and is heavily involved in inflammation and neovascularization [78]. The RAAS pathway begins with the production of preprorenin by the juxtaglomerular cells in the kidney, which is then cleaved into prorenin and released as either prorenin or renin [79,80]. Renin, an aspartyl protease and the rate-limiting enzyme of the RAAS, catalyses the conversion of angiotensinogen to angiotensin I (Ang I). Ang I is subsequently converted by angiotensin-converting enzyme (ACE) into angiotensin II (Ang II) [81–84]. Ang II is a central component of the RAAS and interacts with two primary receptors: the angiotensin type 1 receptor (AT1R) and the angiotensin type 2 receptor (AT2R) [85,86]. Binding of Ang II to AT1R leads to vasoconstriction, inflammation, and neovascularization [87–89]. Additionally, Ang II stimulates the production of aldosterone from the adrenal glands, which plays a crucial role in maintaining fluid homeostasis and further contributes to inflammation and neovascularization through its interaction with the mineralocorticoid receptor [90].

In contrast, the RAAS also includes a protective counter-regulatory axis involving the AT2R and the Mas receptor (MasR) [91]. When Ang II binds to AT2R, it induces vasodilation and exerts anti-fibrotic and anti-inflammatory effects [92]. ACE2, an ACE homologue, converts Ang I to Ang (1–9) and Ang II to Ang (1–7), with the latter binding to AT2R and MasR to counteract the effects of AT1R [93–100]. Recent research has uncovered a novel RAAS pathway involving the (pro)renin receptor [(P)RR], which binds both renin and prorenin independently of Ang II. Activation of the (P)RR pathway triggers inflammatory responses and has been implicated in tumorigenesis [101–106].

Fig. 2 offers an overview on the mechanistic pathways of the classical RAAS.

3.2. The ocular RAAS and related mechanistic pathways

A tissue-specific RAAS has been identified in various human organs, including the eye [25]. Key components of the RAAS have been detected in ocular structures such as the retina and ciliary body, suggesting the potential for targeting these agents to treat ocular disorders [12,14,107–115]. Notably, the blood-retinal barrier prevents circulating RAAS components from entering ocular tissues [13]. However, significant concentrations of critical RAAS agents, such as angiotensin II (Ang II), have been found in ocular tissues, indicating local synthesis and expression of an ocular RAAS [25,110,115,116]. Furthermore, components of the RAAS counter-regulatory arm have been identified in the eye, potentially playing roles in conditions such as diabetic retinopathy and glaucoma [117,118]. Substantial evidence supports the existence of an independent ocular RAAS. The following sections describe the main signalling pathways of key RAAS effectors, including prorenin, angiotensin, and aldosterone.

3.2.1. The (pro)renin pathway

In the eye, the (pro)renin receptor [(P)RR] interacts with prorenin, initiating both RAAS-dependent and RAAS-independent pathways [119–121]. This interaction triggers the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, which in turn modulates the expression of pathogenic agents such as monocyte chemotactic protein (MCP)-1 and intercellular adhesion molecule (ICAM)-1 [122,123]. The RAAS-independent pathway, also known as the receptor-associated prorenin system (RAPS), further activates the expression of

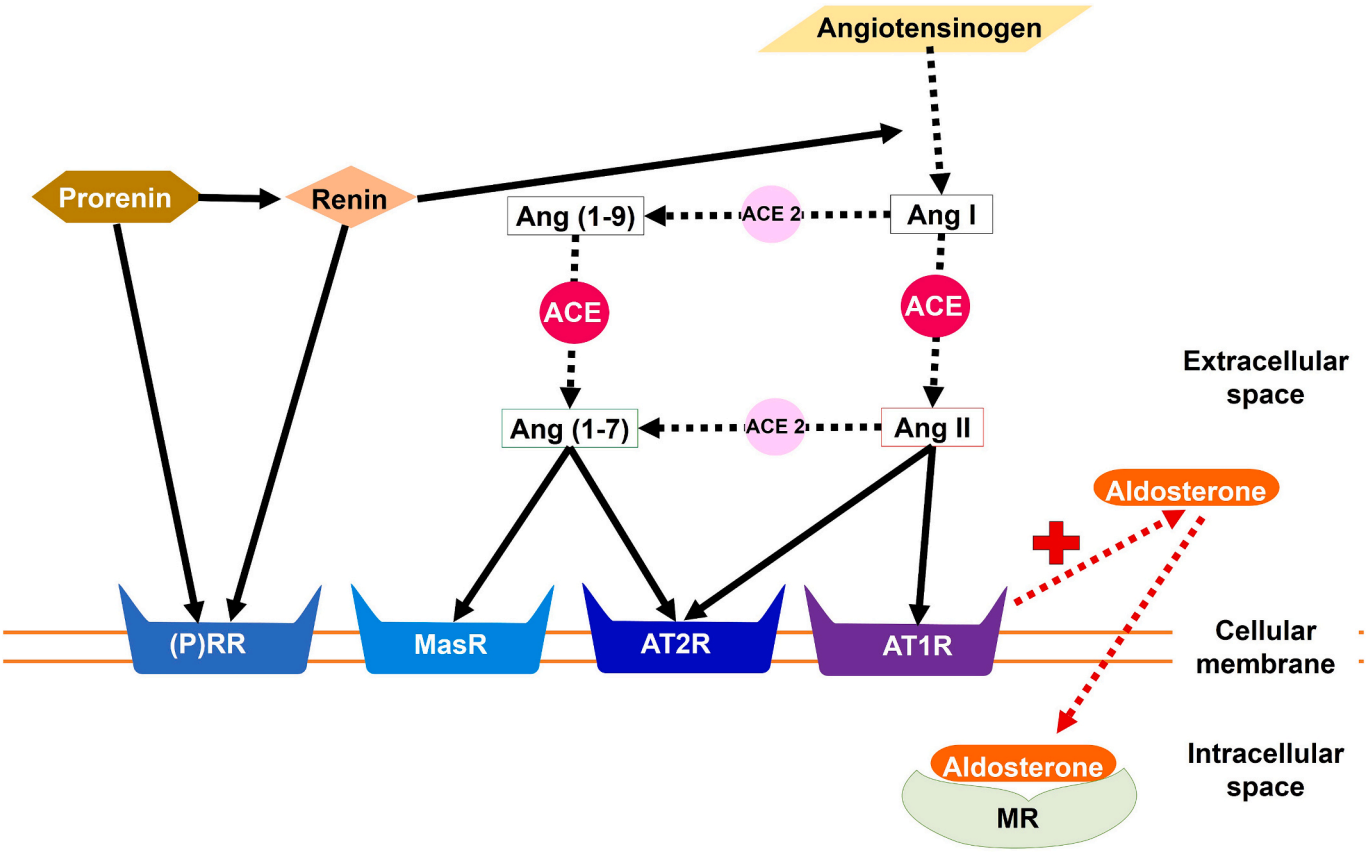


Fig. 2. Overview on the main pathways of the classical RAAS. ACE: angiotensinogen converting enzyme; Ang: angiotensin. ATR: angiotensin II receptor; MasR: Mas Receptor; MR: mineralocorticoid receptor; (P)RR: (pro)renin receptor.

transforming growth factor-beta 1 (TGF-β1) and extracellular matrix proteins like type I collagen and fibronectin. This activation has been observed in hypertensive animal models and contributes to fibrosis [124–127]. In addition, Fu and colleagues have determined that the (P)RR pathway triggers the NOX4/NF-kB axis, inducing endothelial dysfunction via activation of the AT1R cascade [128]. Regarding glaucoma, a recent study suggested the contribution of RAPS, showing that (pro)renin-related stimulation of TM cells ultimately induces tissue remodelling in the TM. This process is possibly connected with the molecular pathogenesis of POAG and neovascular glaucoma [129].

3.2.2. The angiotensin pathway

When Ang II binds to the AT1R receptor, it activates a series of intracellular cascades via phospholipase C (PLC). This activation leads to the stimulation of the inositol-1,4,5-triphosphate (IP3)/Ca^{2+} axis and the diacylglycerol/protein kinase C (DAG/PKC) pathway [12,130–132]. These pathways promote inflammatory and angiogenic responses by inducing the synthesis of mediators such as TGF-β1, VEGF, ICAM-1, MMPs, and NOX, which contribute to inflammation, oxidative stress, and fibrosis [133–140]. Ang II-related oxidative stress, in particular, has been shown to cause endothelial dysfunction in murine ophthalmic arteries through the activation of AT1R and NOX2-dependent ROS formation. Blocking the AT1R and NOX2 pathway may therefore help restore endothelial function in ocular microvasculature compromised by ocular diseases [21].

In contrast, AT2R signalling, activated by Ang II or Ang (1–7), induces vasodilation and exhibits anti-fibrotic, anti-inflammatory, and antioxidant effects, possibly via the phospholipase A2/cyclic guanylate monophosphate/nitric oxide axis [25,141–143]. This pathway suppresses Ang II-related NF-kB activation and ROS formation. However, AT2R also influences angiogenesis through VEGF release [144,145].

The Mas receptor (MasR), another G protein-coupled receptor found in the eye, binds Ang (1–7) and has anti-inflammatory and anti-fibrotic effects [146,147]. Although specific ocular studies on MasR are limited, it is known to generally attenuate ERK1/2 axis activation induced by Ang (1–7) binding to AT1R. This modulation occurs via $G_{\alpha i}$-adenylyl cyclase and leads to decreased NF-kB activation [148–150]. MasR also suppresses the SMAD2 pathway, which reduces TGF-β1 expression and fibrogenesis [151]. Additionally, MasR has anti-proliferative and anti-tumorigenic effects by downregulating the PI3K/Akt/mTOR signalling pathway [152]. Interestingly, Vaajanen and co-workers determined that in the normotensive rabbit eye, topical administration of Ang (1–7) caused a significant decrease in IOP, which was completely blocked by the MasR antagonist (A-779), suggesting the possible activation of MasR triggered by the Ang (1–7) [153].

3.2.3. The aldosterone pathway

Aldosterone binds to the mineralocorticoid receptor, a classical steroid hormone receptor in the nuclear receptor subfamily 3. Upon binding, the aldosterone-mineralocorticoid receptor complex translocates to the cell nucleus, where it initiates the transcription of genes crucial for maintaining fluid homeostasis [154,155]. Preclinical studies have indicated that aldosterone induces 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 glial Müller cells [156]. Additionally, aldosterone has been implicated in choroidal thickening, vasodilation, and leakage, potentially mediated through the small conductance calcium-activated potassium channel 3 (KCa2.3) in choroidal endothelial cells [157]. Furthermore, aldosterone promotes oxidative stress by enhancing the transcription and plasma membrane translocation of pro-oxidative agents, including components of the NADPH oxidase complex such as NOX2 and NOX4 in endothelial cells, leading to an accumulation of ROS [158,159]. In addition, aldosterone has been implicated in processes of inflammation and neovascularization in the retina, possibly via an upregulation of TNF-α, ICAM-1 and VCAM-1 [160,161].

Fig. 3 illustrates the main intracellular cascades activated by the ocular RAAS.

4. Pathophysiological role of the ocular RAAS in glaucoma

4.1. The RAAS and glaucoma pathogenesis: general concepts

While the impact of antihypertensive medications on the risk of intraocular pressure (IOP) elevation and glaucoma onset remains debated [162,163], targeting the renin-angiotensin-aldosterone system (RAAS) has emerged as a potential strategy to manage glaucoma progression. The ocular RAAS is implicated in the regulation of aqueous humor dynamics [164], with components detected in critical ocular structures involved in glaucoma pathophysiology, as evidenced by studies on human non-pigmented ciliary epithelial cells [165,166]. Angiotensin II (Ang II) synthesis may occur within retinal glial cells, supported by the presence of angiotensinogen mRNA in rat retinal glia [167]. Physiologically, Ang II plays a central role in retinal vascular constriction and regulates glial cell and neural function [168,169]. However, in glaucoma, an enhanced activation of the AT1R pathway may augment aqueous humor production, modulate uveoscleral outflow, and consequently elevate IOP [30,170–172]. Thus, suppression of RAAS activity, such as through ACE inhibition or AT1R blockade, may offer therapeutic benefits in managing glaucoma [173]. In animal models, ACE inhibition not only prevents bradykinin breakdown and stimulates prostaglandin production but also reduces IOP by enhancing uveoscleral outflow [174–177]. Additionally, ACE inhibitors lower Ang II levels in aqueous humor, decrease blood flow in the ciliary body, and reduce aqueous humor formation [178,179]. In animal and human studies, AT1R blockade has also been shown to increase uveoscleral outflow and mitigate retinal ganglion cell loss [42,171,172,180].

Furthermore, in vitro investigations have indicated that ACE2 and its product Ang (1–7), which predominantly act through the Mas receptor, exert vasodilatory, antiproliferative, and antifibrotic effects [181,182]. Supporting this, animal studies demonstrate that Ang (1–7) and the ACE2 activator diminazene aceturate can lower IOP, suggesting novel avenues for glaucoma management [44,153,183]. Fig. 4 illustrates the principal mechanistic pathways through which RAAS components contribute to glaucoma pathogenesis, highlighting potential therapeutic targets.

4.2. Targeting oxidative stress and remodelling in POAG using RAAS modulators

Recent studies have highlighted the pathogenic pathways activated by Ang II, which induce oxidative and fibrotic processes in TM cells. An intriguing in vitro study by Li and colleagues on cultured human TM cells revealed that elevated levels of Ang II significantly contribute to the pathophysiology of POAG by upregulating genes such as Col1, FN, and αSMA. These genes encode collagen type I, fibronectin, and alpha-smooth muscle actin, respectively, which are all involved in the fibrogenetic process via a NOX4/ROS axis in cooperation with the SMAD3/TGFβ pathway. Interestingly, the NOX4 inhibitor GLX351322 was found to mitigate Ang II-related fibrogenesis [184]. Additionally, an in vitro investigation by Kim et al. on human Tenon fibroblasts found that irbesartan, an AT1R blocker, effectively suppressed fibroblast migration and ROS production, further reducing cell number and morphological alterations [185]. Moreover, in human Tenon fibroblasts, Ye et al. demonstrated that isoliquiritigenin, a flavonoid with antioxidant activity [186], counteracted Ang II-related fibrogenesis by inhibiting the NF-κB/PPARγ inflammatory pathway [187]. An animal study by Shi et al. demonstrated that following trabeculectomy—a surgical intervention for glaucoma that enhances aqueous humor outflow—increased levels of Ang II in Tenon's capsule fibroblasts led to fibroblast proliferation, migration, and a phenotype transition to myofibroblasts, with an upregulation of genes like *FN* and *αSMA* [188].

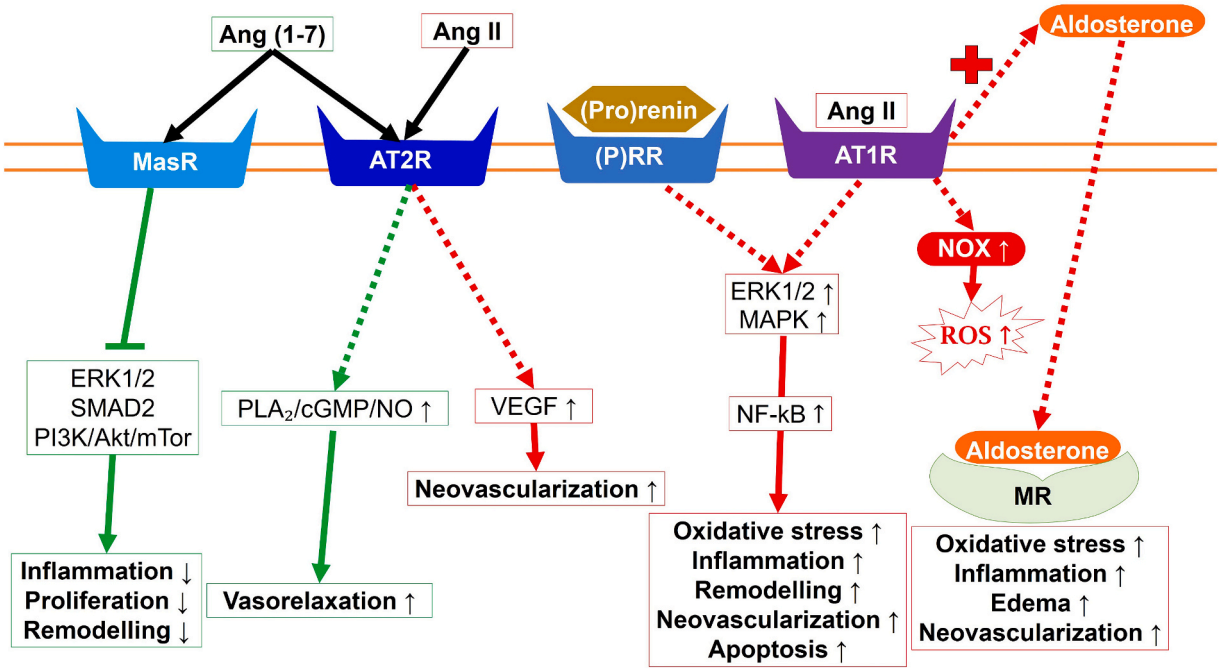


Fig. 3. Overview on the main pathways of the ocular RAAS. The green arrows indicate the beneficial effect in contrasting glaucoma progression, while the red arrows show the detrimental effect that favours the disease. Ang: angiotensin. AT: angiotensin II receptor; cGMP: cyclic guanosine monophosphate; ERK: extracellular signal-regulated kinase; MAPK: mitogen-activated protein kinase; MasR: Mas Receptor; MR: mineralocorticoid receptor; mTOR: mammalian target of rapamycin; NF-kB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NO: nitric oxide; NOX: nicotinamide adenine dinucleotide phosphate oxidase; PI3K: phosphoinositide 3-kinase; PLA_2: phospholipase A2; (P)RR: (pro)renin receptor; ROS: reactive oxygen species; SMAD: suppressor of mothers against decapentaplegic; VEGF: vascular endothelial growth factor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

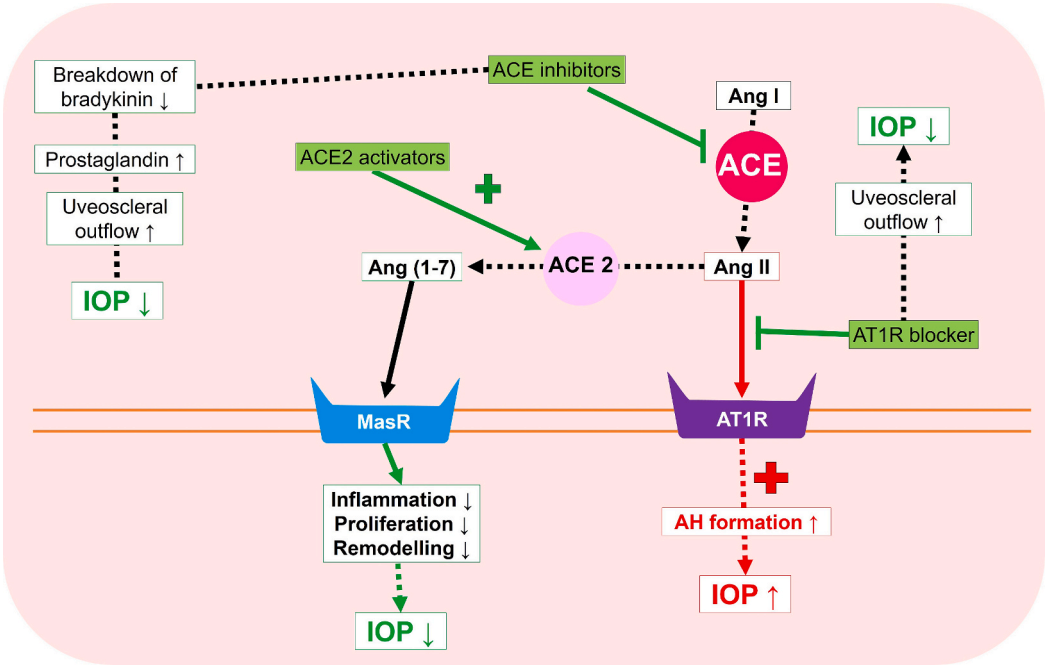


Fig. 4. Illustration of the main effects of the ocular RAAS on the ciliary body, its influence on the aqueous humor formation and representation of the mechanism of action of RAAS modulators, attenuating IOP. ACE: angiotensin-converting enzyme; Ang: angiotensin; AH: aqueous humor; AT1R: angiotensin II type 1 receptors; IOP: intraocular pressure; MasR: Mas receptor.

In addition to the AT1R, another promising target within the ocular RAAS for POAG treatment may be the (P)RR. In vitro, animal, and human studies have highlighted the significant role of (P)RR in ocular inflammation, fibrosis, and retinal neovascularization [119,120,189–197]. Notably, an in vitro investigation determined that direct renin inhibitors and other RAAS modulators do not act upstream of the (P)RR, and therefore do not affect the RAAS-independent pathways [198]. This underscores the potential for designing specific drugs to directly suppress (P)RR in ocular disorders. Building on this knowledge, Ishizuka and associates demonstrated in surgical samples from

patients with POAG that prorenin stimulation in human TM cells upregulates cell junction constituents like connexin 43 and zona occludens 1 while downregulating tissue plasminogen activator. These effects were reversed by (P)RR inhibitors, the decoy peptides NH2-RIFLKRMPSI-COOH, collectively underscoring the involvement of (P)RR in the pathogenesis of POAG via TM tissue remodelling [129].

Fig. 5 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.

4.3. Significance of AngII and aldosterone in the pathogenesis of NTG

Ang II plays a crucial role in the pathogenesis of NTG. Ozawa et al. demonstrated that in cultured RGCs, oxidative stress-induced cell death via the AT1R axis could be mitigated by telmisartan, an AT1R blocker [199]. In addition, in vitro and in vivo 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 as part of a feedback mechanism, subsequently elevating Ang II levels, which may adversely affect RGCs by inducing glial inflammation [200,201]. In an animal study, 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 oxidative stress-induced RGC death. However, candesartan suppressed iNOS overexpression and subsequent ROS excess by inhibiting the TLR4–ASK1 pathway, effectively protecting RGCs [202].

Since vascular dysregulation and hypotension are recognized risk factors for NTG, Jeon et al. found significantly higher systemic concentrations and variability of renin in NTG patients compared to control subjects [203]. Further research by the same group compared glaucoma models of ocular hypertensive rats with systemic hypotensive rats, revealing higher levels of Ang II and increased expression of its receptors in both serum and retina of systemic hypotensive rats. These rats also exhibited glial activation and necroptosis in RGCs via elevated tumor necrosis factor α (TNF-α) and receptor-interacting protein 3 (RIP3), and decreased inactive caspase 8 [43]. Interestingly, this Ang II-glial activation axis was specific to systemic hypotension, as JNK and RIP3 inhibitors could reverse RGC death in hypotensive but not hypertensive rats [43]. Moreover, Oh et al. recently demonstrated in a systemic hypotensive rat model that both AT1R and AT2R 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 [204]. They also found a correlation between fibroblast activation and RGC death, which was reversed by sub-Tenon injection of an AT1R blocker, losartan, suggesting that inhibition of Ang II may suppress scleral fibrogenesis, ultimately protecting RGCs [204].

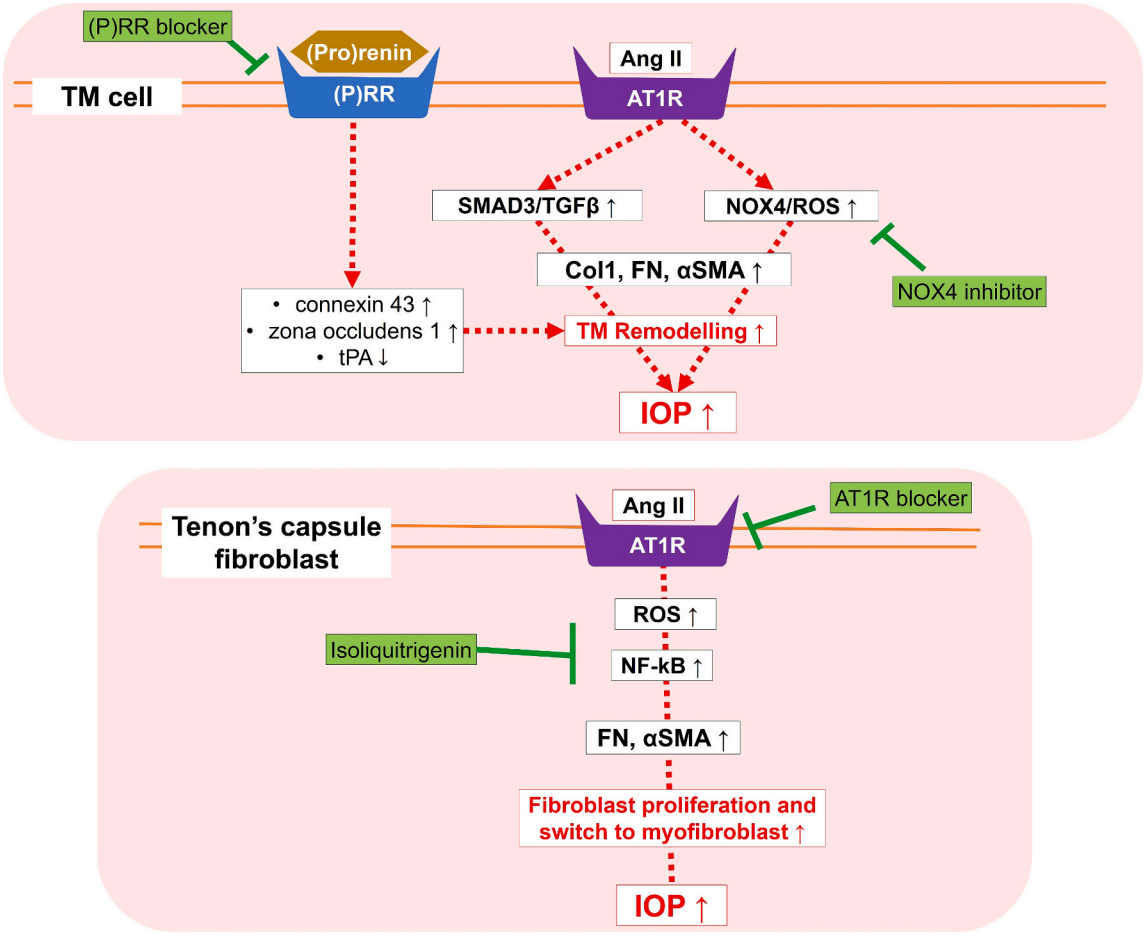


Fig. 5. Schematic representation of the effect of the ocular RAAS on trabecular meshwork and Tenon's capsule fibroblasts, and action of RAAS modulators and antioxidants antagonizing oxidative stress and raised IOP during POAG. αSMA: α-smooth muscle actin; Ang: angiotensin; AQ: aqueous humor; AT1R: angiotensin II type 1 receptors; Col1: collagen type 1; FN: fibronectin; IOP: intraocular pressure; NF-kB: nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NOX: nicotinamide adenine dinucleotide phosphate oxidase; (P)RR: (pro)renin receptor; ROS: reactive oxygen species; SMAD3: suppressor of mothers against decapentaplegic type 3; TGF-β: transforming growth factor β; TM: trabecular meshwork.

Aldosterone has also been implicated in the pathogenesis of NTG. Studies have identified its role in inflammation, neovascularization, and retinal vascular dysfunction in disorders such as age-related macular degeneration [38,205]. Studies in rats showed that systemic administration of aldosterone led to progressive RGC loss and glaucomatous optic neuropathy without elevated IOP, suggesting the role of aldosterone in NTG pathophysiology [206,207]. Recently, Wada et al. reported that systemic aldosterone administration in rats resulted in decreased optic nerve head perfusion and RGC loss, following retinal vessel constriction without changes in IOP or blood pressure [208]. The current literature has reported that elevated plasma aldosterone levels can be considered as a risk factor for developing NTG [209]. In a clinical study, Ohshima and colleagues demonstrated a higher frequency of retinal nerve fibre layer defects in patients with primary aldosteronism compared to controls [210]. Ono and colleagues assessed gene expression changes in the retina after systemic aldosterone administration, finding upregulation of genes such as PF4, which encodes platelet factor 4, involved in ROS release via NOX activity, suggesting that RGC loss may be linked to ocular blood abnormalities due to endothelial cell apoptosis caused by PF4 upregulation. In addition, the authors reported on other upregulated genes that also may have a relevant role in the aldosterone-induced effect on retinal perfusion and endothelial cell apoptosis via NOX, such as the cyclin-dependent kinase inhibitor 1 A (*Cdkn1a*) and the vitamin D receptor (*Vdr*) [211].

Considering the pathophysiological relevance of aldosterone in many ocular disorders, pharmacological blockade of the mineralocorticoid receptor has been tested in ophthalmology to counteract disease progression. For example, recent investigations have demonstrated the effectiveness of finerenone in combating diabetic retinopathy [32,212]. However, the use of eplerenone for treating central serous chorioretinopathy is currently not recommended [213,214]. Interestingly, a very recent retrospective study on 41 patients with glaucoma found that eplerenone was effective in decreasing IOP in a dose-dependent manner. The study speculated that the retinal pigment epithelium cell pumps responsible for the posterior flow of aqueous humor might be regulated via the mineralocorticoid receptor [215].

Fig. 6 summarizes diverse pathways that lead to RGC loss trough the action of RAAS components in the retinal glia during NTG.

5. Future directions and conclusions

Recent findings on the potential for blocking the RAAS in glaucoma have illuminated pathogenetic events such as fibrogenesis, glial activation, inflammation, and the establishment of oxidative stress. These processes, relevant in wound healing after glaucoma filtration surgeries, can be effectively countered by molecules like the antioxidant flavonoid isoliquiritigenin, ACE inhibitors such as captopril, or AT1R blockers like losartan and candesartan. However, these recent pre-clinical investigations require further exploration to confirm the results and potentially validate these novel treatment strategies in large clinical

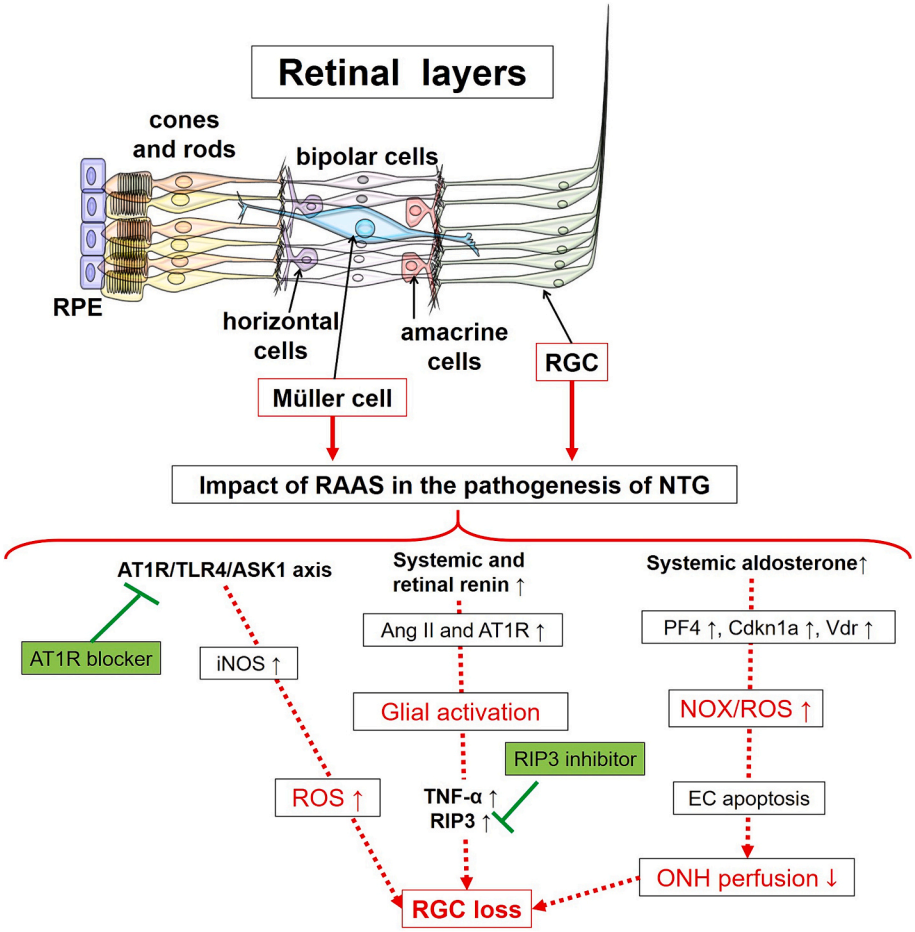


Fig. 6. Illustration of the retinal layers and of the impact of the ocular RAAS in the pathogenesis of NTG. Ang: angiotensin; ASK1: apoptosis signal-regulating kinase 1; AT1R: angiotensin II receptor type 1; Cdkn1a: cyclin-dependent kinase inhibitor 1 A; EC: endothelial cell; iNOS: inducible nitric oxide synthase; NOX: nicotinamide adenine dinucleotide phosphate oxidase; NTG: normal tension glaucoma; ONH: optic nerve head; PF4: platelet factor 4; RIP3: receptor interacting protein 3; RGC: retinal ganglion cell; RPE: retinal pigment epithelium; ROS: reactive oxygen species; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor α; Vdr: vitamin D receptor.

studies. Of note, from a pharmacological perspective, topical RAAS modulators can achieve higher concentrations in ocular tissues and have fewer systemic effects compared to systemic administration. However, systemic compounds may also be effective if they are able to cross the blood-retinal barrier.

Our understanding of the role of aldosterone in the pathogenesis of NTG is limited. A key question remains whether modulating MR activation in glaucoma could benefit patients, necessitating further research. Another important area for exploration is the use of novel RAAS modulators, such as (P)RR blockers and ACE2 activators, in glaucoma. This research field is still relatively new in ophthalmology and requires cautious and robust validation.

In summary, our review has compiled a comprehensive and updated overview of the role of RAAS in glaucoma, highlighting its interconnection with oxidative stress, inflammation, and remodelling. We have examined the main cellular cascades triggered by RAAS, reporting on the benefits of employing RAAS modulators to counteract glaucomatous progression. These 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.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Francesco Buonfiglio: Writing – original draft, Visualization, Conceptualization. **Norbert Pfeiffer:** Writing – review & editing. **Adrian Gericke:** Writing – review & editing, Supervision, Conceptualization.

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 paper.

Data availability

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

References

[1] S.R. Flaxman, R.R.A. Bourne, S. Resnikoff, P. Ackland, T. Braithwaite, M. V. Cicinelli, A. Das, J.B. Jonas, J. Keeffe, J.H. Kempen, J. Leasher, H. Limburg, K. Naidoo, K. Pesudovs, A. Silvester, G.A. Stevens, N. Tahhan, T.Y. Wong, H. R. Taylor, Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis, Lancet Glob. Health 5 (12) (2017) e1221–e1234, https://doi.org/10.1016/s2214-109x(17)30393-5.

[2] H.A. Quigley, A.T. Broman, The number of people with glaucoma worldwide in 2010 and 2020, Br. J. Ophthalmol. 90 (3) (2006) 262–267, https://doi.org/10.1136/bjo.2005.081224.

[3] Y.C. Tham, X. Li, T.Y. Wong, H.A. Quigley, T. Aung, C.Y. Cheng, Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis, Ophthalmology 121 (11) (2014) 2081–2090, https://doi.org/10.1016/j.ophtha.2014.05.013.

[4] N. Zhang, J. Wang, Y. Li, B. Jiang, Prevalence of primary open angle glaucoma in the last 20 years: a meta-analysis and systematic review, Sci. Rep. 11 (1) (2021) 13762, https://doi.org/10.1038/s41598-021-92971-w.

[5] T.S. Acott, K.E. Keller, M.J. Kelley, Role of Proteoglycans in the Trabecular Meshwork☆, Reference Module in Neuroscience and Biobehavioral Psychology, Elsevier, 2017, https://doi.org/10.1016/B978-0-12-809324-5.01518-2.

[6] M. Cesareo, C. Giannini, A. Martucci, M. Di Marino, G. Pocobelli, F. Aiello, R. Mancino, C. Nucci, Chapter 2 - links between obstructive sleep apnea and glaucoma neurodegeneration, in: G. Bagetta, C. Nucci (Eds.), Progress in Brain Research, Elsevier, 2020, pp. 19–36, https://doi.org/10.1016/bs.pbr.2020.07.010.

[7] P.R. Lichter, Glaucoma clinical trials and what they mean for our patients, Am. J. Ophthalmol. 136 (1) (2003) 136–145, https://doi.org/10.1016/s0002-9394(03)00143-0.

[8] P.P. Chen, Blindness in patients with treated open-angle glaucoma, Ophthalmology 110 (4) (2003) 726–733, https://doi.org/10.1016/s0161-6420(02)01974-7.

[9] Y.H. Kwon, C.S. Kim, M.B. Zimmerman, W.L. Alward, S.S. Hayreh, Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma, Am. J. Ophthalmol. 132 (1) (2001) 47–56, https://doi.org/10.1016/s0002-9394(01)00912-6.

[10] L. Rossetti, M. Digiuni, G. Montesano, M. Centofanti, A.M. Fea, M. Iester, P. Frezzotti, M. Figus, A. Ferreras, F. Oddone, L. Tanga, T. Rolle, V. Battaglino, C. Posarelli, I. Motolese, P. Mittica, S.A. Bagaglia, C. Menicacci, S. De Cilla, A. Autelitano, P. Fogagnolo, Blindness and Glaucoma: a multicenter data review from 7 academic eye clinics, PLoS One 10 (8) (2015) e0136632, https://doi.org/10.1371/journal.pone.0136632.

[11] F. Buonfiglio, N. Pfeiffer, A. Gericke, Immunomodulatory and antioxidant drugs in Glaucoma treatment, Pharmaceuticals 16 (9) (2023) 1193, https://doi.org/10.3390/ph16091193.

[12] A.J. White, S.C. Cheruvu, M. Sarris, S.S. Liyanage, E. Lumbers, J. Chui, D. Wakefield, P.J. McCluskey, Expression of classical components of the renin-angiotensin system in the human eye, J. Renin-Angiotensin-Aldosterone Syst. 16 (1) (2015) 59–66, https://doi.org/10.1177/1470320314549791.

[13] A. Danser, F. Derkx, P. Admiraal, J. Deinum, P. De Jong, M. Schalekamp, Angiotensin levels in the eye, Invest. Ophthalmol. Vis. Sci. 35 (3) (1994) 1008–1018. https://www.ncbi.nlm.nih.gov/pubmed/8125711.

[14] E. Savaskan, K.U. Löffler, F. Meier, F. Müller-Spahn, J. Flammer, P. Meyer, Immunohistochemical localization of angiotensin-converting enzyme, angiotensin II and AT1 receptor in human ocular tissues, Ophthalmic Res. 36 (6) (2004) 312–320, https://doi.org/10.1159/000081633.

[15] S. Rajagopalan, S. Kurz, T. Münzel, M. Tarpey, B.A. Freeman, K.K. Griendling, D. G. Harrison, Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone, J. Clin. Invest. 97 (8) (1996) 1916–1923, https://doi.org/10.1172/JCI118623.

[16] L.M. Willis, A.B. El-Remessy, P.R. Somanath, D.L. Deremer, S.C. Fagan, Angiotensin receptor blockers and angiogenesis: clinical and experimental evidence, Clin. Sci. 120 (8) (2011) 307–319, https://doi.org/10.1042/cs20100389.

[17] C.J. Moravski, D.J. Kelly, M.E. Cooper, R.E. Gilbert, J.F. Bertram, S. Shahinfar, S. L. Skinner, J.L. Wilkinson-Berka, Retinal neovascularization is prevented by blockade of the renin-angiotensin system, Hypertension 36 (6) (2000) 1099–1104, https://doi.org/10.1161/01.hyp.36.6.1099.

[18] D. Wang, Y. Chen, T. Chabrashvili, S. Aslam, L.J.B. Conde, J.G. Umans, C. S. Wilcox, Role of oxidative stress in endothelial dysfunction and enhanced responses to angiotensin II of afferent arterioles from rabbits infused with angiotensin II, J. Am. Soc. Nephrol. 14 (11) (2003) 2783–2789, https://doi.org/10.1097/01.asn.0000090747.59919.d2.

[19] J.R. Gomolak, S.P. Didion, Angiotensin II-induced endothelial dysfunction is temporally linked with increases in interleukin-6 and vascular macrophage accumulation, Front. Physiol. 5 (2014) 115951, https://doi.org/10.3389/fphys.2014.00396.

[20] Z. Zhang, M. Wang, S.-J. Xue, D.-H. Liu, Y.-B. Tang, Simvastatin ameliorates angiotensin II-induced endothelial dysfunction through restoration of rho-BH4-eNOS-NO pathway, Cardiovasc. Drugs Ther. 26 (2012) 31–40, https://doi.org/10.1007/s10557-011-6351-3.

[21] M. Birk, E. Baum, J.K. Zadeh, C. Manicam, N. Pfeiffer, A. Patzak, J. Helmstädter, S. Steven, M. Kuntic, A. Daiber, A. Gericke, Angiotensin II induces oxidative stress and endothelial dysfunction in mouse ophthalmic arteries via involvement of AT1 receptors and NOX2, Antioxidants 10 (8) (2021) 1238, https://doi.org/10.3390/antiox10081238.

[22] P. Rong, J.L. Wilkinson-Berka, S.L. Skinner, Control of renin secretion from adrenal gland in transgenic Ren-2 and normal rats, Mol. Cell. Endocrinol. 173 (1–2) (2001) 203–212, https://doi.org/10.1016/s0303-7207(00)00406-8.

[23] J.L. Wilkinson-Berka, D.J. Kelly, P. Rong, D.J. Campbell, S.L. Skinner, Characterisation of a thymic renin–angiotensin system in the transgenic m (Ren-2) 27 rat, Mol. Cell. Endocrinol. 194 (1–2) (2002) 201–209, https://doi.org/10.1016/s0303-7207(02)00217-4.

[24] T. Kurihara, Y. Ozawa, S. Ishida, H. Okano, K. Tsubota, Renin-angiotensin system hyperactivation can induce inflammation and retinal neural dysfunction, Int. J. Inflamm. 2012 (2012), https://doi.org/10.1155/2012/581695.

[25] R. Choudhary, M.S. Kapoor, A. Singh, S.H. Bodakhe, Therapeutic targets of renin-angiotensin system in ocular disorders, J. Curr. Ophthalmol. 29 (1) (2017) 7–16, https://doi.org/10.1016/j.joco.2016.09.009.

[26] N. Nagai, H. Kawashima, E. Toda, K. Homma, H. Osada, N.A. Guzman, S. Shibata, Y. Uchiyama, H. Okano, K. Tsubota, Y. Ozawa, Renin-angiotensin system impairs macrophage lipid metabolism to promote age-related macular degeneration in mouse models, Commun. Biol. 3 (1) (2020) 767, https://doi.org/10.1038/s42003-020-01483-2.

[27] C. Ren, W. Liu, X. Yin, B. Zhang, P. Lu, Renin-angiotensin system inhibitor usage and age-related macular degeneration among hypertensive patients: results from the National Health and nutrition examination survey, 2005-2008, J. Ophthalmol. 2020 (2020) 4252031, https://doi.org/10.1155/2020/4252031.

[28] V.B.B. Seki, G.R. Souza, A. Messias, D.E. Casarini, J.S. Paula, Aqueous humor renin, angiotensin I, and angiotensin II activity in primary open-angle glaucoma,

Arq. Bras. Oftalmol. 83 (4) (2020) 318–322, https://doi.org/10.5935/0004-2749.20200052.
[29] S.J. Jeon, H.B. Hwang, N.Y. Lee, Evaluation of systemic renin and angiotensin II levels in Normal tension Glaucoma, J. Clin. Med. 9 (12) (2020), https://doi.org/10.3390/jcm9123838.
[30] K. Semba, Inhibition of renin-angiotensin system prevents neurodegeneration in a mouse model of Normal tension Glaucoma, Nippon Ganka Gakkai Zasshi 120 (11) (2016) 772–782. https://www.ncbi.nlm.nih.gov/pubmed/30074742.
[31] R. Prasad, J.L. Floyd, M. Dupont, A. Harbour, Y. Adu-Agyeiwaah, B. Asare-Bediako, D. Chakraborty, K. Kichler, A. Rohella, S. Li Calzi, R. Lammendella, J. Wright, M.E. Boulton, G.Y. Oudit, M.K. Raizada, B.R. Stevens, Q. Li, M.B. Grant, Maintenance of enteral ACE2 prevents diabetic retinopathy in type 1 diabetes, Circ. Res. 132 (1) (2023) e1–e21, https://doi.org/10.1161/circresaha.122.322003.
[32] J.R. Jerome, D. Deliyanti, V. Suphapimol, P. Kolkhof, J.L. Wilkinson-Berka, Finerenone, a non-steroidal mineralocorticoid receptor antagonist, reduces vascular injury and increases regulatory T-cells: studies in rodents with diabetic and Neovascular retinopathy, Int. J. Mol. Sci. 24 (3) (2023), https://doi.org/10.3390/ijms24032334.
[33] R. Choudhary, J. Shree, A. Singh, S.H. Bodakhe, Role of the renin-angiotensin system in the development of cataract formation in angiotensin-II-induced experimental rats, J. Biochem. Mol. Toxicol. 35 (7) (2021) e22789, https://doi.org/10.1002/jbt.22789.
[34] J. Shree, R. Choudhary, S.H. Bodakhe, Therapeutic effects of various renin angiotensin modulators on hyperglycemia-induced cataract formation in Sprague Dawley rats, Eur. J. Ophthalmol. 31 (5) (2021) 2360–2369, https://doi.org/10.1177/1120672120962401.
[35] M. Nath, P. Chandra, N. Halder, B. Singh, A.K. Deorari, A. Kumar, R. Azad, T. Velpandian, Involvement of renin-angiotensin system in retinopathy of prematurity - a possible target for therapeutic intervention, PLoS One 11 (12) (2016) e0168809, https://doi.org/10.1371/journal.pone.0168809.
[36] L.A. Katargina, N.B. Chesnokova, T.A. Pavlenko, O.V. Beznos, N.A. Osipova, A. Y. Panova, Enalaprilat as a new means of preventing the development of retinopathy of prematurity, Biomed. Khim. 69 (2) (2023) 97–103, https://doi.org/10.18097/pbmc20236902097.
[37] E. Abdelhakeem, M. El-Nabarawi, R. Shamma, Eplerenone repurposing in management of chorioretinopathy: mechanism, nanomedicine-based delivery applications and future trends, Br. J. Clin. Pharmacol. 88 (6) (2022) 2665–2672, https://doi.org/10.1111/bcp.15213.
[38] M.J. Allingham, P.S. Mettu, S.W. Cousins, Aldosterone as a mediator of severity in retinal vascular disease: evidence and potential mechanisms, Exp. Eye Res. 188 (2019) 107788, https://doi.org/10.1016/j.exer.2019.107788.
[39] Y. Qiu, P.K. Shil, P. Zhu, H. Yang, A. Verma, B. Lei, Q. Li, Angiotensin-converting enzyme 2 (ACE2) activator diminazene aceturate ameliorates endotoxin-induced uveitis in mice, Invest. Ophthalmol. Vis. Sci. 55 (6) (2014) 3809–3818, https://doi.org/10.1167/iovs.14-13883.
[40] A. Miyazaki, N. Kitaichi, K. Ohgami, D. Iwata, X.H. Jin, K. Iwabuchi, T. Morohashi, S. Ohno, K. Onoé, Anti-inflammatory effect of angiotensin type 1 receptor antagonist on endotoxin-induced uveitis in rats, Graefes Arch. Clin. Exp. Ophthalmol. 246 (5) (2008) 747–757, https://doi.org/10.1007/s00417-007-0730-2.
[41] Y. Qiu, L. Tao, S. Zheng, R. Lin, X. Fu, Z. Chen, C. Lei, J. Wang, H. Li, Q. Li, B. Lei, AAV8-mediated angiotensin-converting enzyme 2 gene delivery prevents experimental autoimmune uveitis by regulating MAPK, NF-κB and STAT3 pathways, Sci. Rep. 6 (2016) 31912, https://doi.org/10.1038/srep31912.
[42] H.A. Quigley, I.F. Pitha, D.S. Welsbie, C. Nguyen, M.R. Steinhart, T.D. Nguyen, M. E. Pease, E.N. Oglesby, C.A. Berlinicke, K.L. Mitchell, J. Kim, J.J. Jefferys, E. C. Kimball, Losartan treatment protects retinal ganglion cells and alters scleral remodeling in experimental Glaucoma, PLoS One 10 (10) (2015) e0141137, https://doi.org/10.1371/journal.pone.0141137.
[43] S.J. Jeon, J. Huh, E. Jeong, C.K. Park, H.Y.L. Park, Angiotensin II related glial cell activation and necroptosis of retinal ganglion cells after systemic hypotension in glaucoma, Cell Death Dis. 13 (4) (2022) 323, https://doi.org/10.1038/s41419-022-04762-4.
[44] G. Foureaux, J.C. Nogueira, B.S. Nogueira, G.O. Fulgêncio, G.B. Menezes, S. O. Fernandes, V.N. Cardoso, R.S. Fernandes, G.P. Oliveira, J.R. Franca, A. A. Faraco, M.K. Raizada, A.J. Ferreira, Antiglaucomatous effects of the activation of intrinsic angiotensin-converting enzyme 2, Invest. Ophthalmol. Vis. Sci. 54 (6) (2013) 4296–4306, https://doi.org/10.1167/iovs.12-11427.
[45] C. Burgoyne, The morphological difference between glaucoma and other optic neuropathies, J. Neuroophthalmol. 35 (Suppl. 1) (2015) S8–s21, https://doi.org/10.1097/wno.0000000000000289 (0 1).
[46] M. Kroese, H. Burton, Primary open angle glaucoma. The need for a consensus case definition, J. Epidemiol. Community Health 57 (9) (2003) 752–754, https://doi.org/10.1136/jech.57.9.752.
[47] R.J. Casson, G. Chidlow, J.P. Wood, J.G. Crowston, I. Goldberg, Definition of glaucoma: clinical and experimental concepts, Clin. Experiment. Ophthalmol. 40 (4) (2012) 341–349, https://doi.org/10.1111/j.1442-9071.2012.02773.x.
[48] P.J. Foster, R. Buhrmann, H.A. Quigley, G.J. Johnson, The definition and classification of glaucoma in prevalence surveys, Br. J. Ophthalmol. 86 (2) (2002) 238–242, https://doi.org/10.1136/bjo.86.2.238.
[49] B. Khazaeni, L. Khazaeni, Acute Closed Angle Glaucoma, StatPearls, StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC, Treasure Island (FL), 2022.
[50] B.C. Flores-Sánchez, A.J. Tatham, Acute angle closure glaucoma, Br. J. Hosp. Med. (Lond.) 80 (12) (2019) C174–c179, https://doi.org/10.12968/hmed.2019.80.12.C174.
[51] A.K. Schuster, C. Erb, E.M. Hoffmann, T. Dietlein, N. Pfeiffer, The diagnosis and treatment of Glaucoma, Dtsch. Arztebl. Int. 117 (13) (2020) 225–234, https://doi.org/10.3238/arztebl.2020.0225.
[52] V. Andrés-Guerrero, J. García-Feijoo, A.G. Konstas, Targeting Schlemm's canal in the medical therapy of Glaucoma: current and future considerations, Adv. Ther. 34 (5) (2017) 1049–1069, https://doi.org/10.1007/s12325-017-0513-z.
[53] E. Lütjen-Drecoll, Morphological changes in glaucomatous eyes and the role of TGFβ2 for the pathogenesis of the disease, Exp. Eye Res. 81 (1) (2005) 1–4, https://doi.org/10.1016/j.exer.2005.02.008.
[54] K.E. Keller, D.M. Peters, Pathogenesis of glaucoma: extracellular matrix dysfunction in the trabecular meshwork-a review, Clin. Experiment. Ophthalmol. 50 (2) (2022) 163–182, https://doi.org/10.1111/ceo.14027.
[55] E.W. Böhm, F. Buonfiglio, A.M. Voigt, P. Bachmann, T. Safi, N. Pfeiffer, A. Gericke, Oxidative stress in the eye and its role in the pathophysiology of ocular diseases, Redox Biol. 68 (2023) 102967, https://doi.org/10.1016/j.redox.2023.102967.
[56] A. Gericke, C. Mann, J.K. Zadeh, A. Musayeva, I. Wolff, M. Wang, N. Pfeiffer, A. Daiber, H. Li, N. Xia, V. Prokosch, Elevated intraocular pressure causes abnormal reactivity of mouse retinal arterioles, Oxidative Med. Cell. Longev. 2019 (2019) 9736047, https://doi.org/10.1155/2019/9736047.
[57] O.W. Gramlich, S. Beck, N. von Thun und Hohenstein-Blaul, N. Boehm, A. Ziegler, J.M. Vetter, N. Pfeiffer, F.H. Grus, Enhanced Insight into the Autoimmune Component of Glaucoma: IgG Autoantibody Accumulation and Pro-Inflammatory Conditions in Human Glaucomatous Retina, PLoS One 8 (2) (2013) e57557, https://doi.org/10.1371/journal.pone.0057557.
[58] B.W. Martin, T. Gülgün, Y. Junjie, P. Guanghua, V.P. Rajkumar, A. Neeraj, M. S. Rebecca, J.C. David, Induced autoimmunity to heat shock proteins elicits glaucomatous loss of retinal ganglion cell neurons via activated T-cell-derived Fas-ligand, J. Neurosci. 28 (46) (2008) 12085, https://doi.org/10.1523/JNEUROSCI.3200-08.2008.
[59] S.C. Joachim, F.H. Grus, N. Pfeiffer, Analysis of autoantibody repertoires in sera of patients with Glaucoma, Eur. J. Ophthalmol. 13 (9–10) (2003) 752–758, https://doi.org/10.1177/1120672103013009-1003.
[60] S.C. Joachim, J. Reichelt, S. Berneiser, N. Pfeiffer, F.H. Grus, Sera of glaucoma patients show autoantibodies against myelin basic protein and complex autoantibody profiles against human optic nerve antigens, Graefe's archive for, Clin. Experiment. Ophthalmol. 246 (2008) 573–580.
[61] S.C. Joachim, N. Pfeiffer, F.H. Grus, Autoantibodies in patients with glaucoma: a comparison of IgG serum antibodies against retinal, optic nerve, and optic nerve head antigens, Graefe's archive for, Clin. Experiment. Ophthalmol. 243 (2005) 817–823.
[62] F.H. Grus, S.C. Joachim, E.M. Hoffmann, N. Pfeiffer, Complex autoantibody repertoires in patients with glaucoma, Mol. Vis. 10 (1327137) (2004) 13–17.
[63] F. Grus, S. Joachim, M. Wax, N. Pfeiffer, Serum autoantibodies in glaucoma patients from Germany and the United States: further implications for autoimmune mechanisms in the neurodegenerative processes of glaucoma, Invest. Ophthalmol. Vis. Sci. 46 (13) (2005) 1285.
[64] M.B. Wax, G. Tezel, I. Saito, R.S. Gupta, J.B. Harley, Z. Li, C. Romano, Anti-Ro/SS-A positivity and heat shock protein antibodies in patients with normal-pressure glaucoma, Am. J. Ophthalmol. 125 (2) (1998) 145–157.
[65] M.B. Wax, G. Tezel, K. Kawase, Y. Kitazawa, Serum autoantibodies to heat shock proteins in glaucoma patients from Japan and the United States, Ophthalmology 108 (2) (2001) 296–302.
[66] S.C. Joachim, K. Bruns, K.J. Lackner, N. Pfeiffer, F.H. Grus, Antibodies to α B-crystallin, vimentin, and heat shock protein 70 in aqueous humor of patients with normal tension glaucoma and IgG antibody patterns against retinal antigen in aqueous humor, Curr. Eye Res. 32 (6) (2007) 501–509.
[67] K. Bell, C. Wilding, S. Funke, N. Pfeiffer, F.H. Grus, Protective effect of 14-3-3 antibodies on stressed neuroretinal cells via the mitochondrial apoptosis pathway, BMC Ophthalmol. 15 (2015) 1–13.
[68] M. Wang, H. Liu, N. Xia, H. Li, T. van Beers, A. Gericke, V. Prokosch, Intraocular Pressure-induced endothelial dysfunction of retinal blood vessels is persistent, but does not trigger retinal ganglion cell loss, Antioxidants (Basel) 11 (10) (2022), https://doi.org/10.3390/antiox11101864.
[69] D.P. Crabb, N.D. Smith, F.C. Glen, R. Burton, D.F. Garway-Heath, How does glaucoma look?: patient perception of visual field loss, Ophthalmology 120 (6) (2013) 1120–1126, https://doi.org/10.1016/j.ophtha.2012.11.043.
[70] J. Aspberg, A. Heijl, B. Bengtsson, Screening for open-angle Glaucoma and its effect on blindness, Am. J. Ophthalmol. 228 (2021) 106–116, https://doi.org/10.1016/j.ajo.2021.03.030.
[71] J.B. Jonas, W.M. Budde, S. Panda-Jonas, Ophthalmoscopic evaluation of the optic nerve head, Surv. Ophthalmol. 43 (4) (1999) 293–320, https://doi.org/10.1016/s0039-6257(98)00049-6.
[72] B.E. Prum Jr., L.F. Rosenberg, S.J. Gedde, S.L. Mansberger, J.D. Stein, S.E. Moroi, L.W. Herndon Jr., M.C. Lim, R.D. Williams, Primary open-angle Glaucoma preferred practice pattern(®) guidelines, Ophthalmology 123 (1) (2016) P41–p111, https://doi.org/10.1016/j.ophtha.2015.10.053.
[73] P.P. Tan, H.H. Yuan, X. Zhu, Y.Y. Cui, H. Li, X.M. Feng, Y. Qiu, H.Z. Chen, W. Zhou, Activation of muscarinic receptors protects against retinal neurons damage and optic nerve degeneration in vitro and in vivo models, CNS Neurosci. Ther. 20 (3) (2014) 227–236, https://doi.org/10.1111/cns.12187.
[74] G. Li, C. Lee, A.T. Read, K. Wang, J. Ha, M. Kuhn, I. Navarro, J. Cui, K. Young, R. Gorijavolu, T. Sulchek, C. Kopczynski, S. Farsiu, J. Samples, P. Challa, C.

R. Ethier, W.D. Stamer, Anti-fibrotic activity of a rho-kinase inhibitor restores outflow function and intraocular pressure homeostasis, Elife 10 (2021), https://doi.org/10.7554/eLife.60831.
[75] M. Batra, S. Gupta, A.B. Nair, M. Dhanawat, S. Sandal, M.A. Morsy, Netarsudil: a new ophthalmic drug in the treatment of chronic primary open angle glaucoma and ocular hypertension, Eur. J. Ophthalmol. 31 (5) (2021) 2237–2244, https://doi.org/10.1177/11206721211008783.
[76] M.V. Boland, A.-M. Ervin, D.S. Friedman, H.D. Jampel, B.S. Hawkins, D. Vollenweider, Y. Chelladurai, D. Ward, C. Suarez-Cuervo, K.A. Robinson, Comparative effectiveness of treatments for open-angle Glaucoma: a systematic review for the U.S. preventive services task force, Ann. Intern. Med. 158 (4) (2013) 271–279, https://doi.org/10.7326/0003-4819-158-4-201302190-00008.
[77] F. Buonfiglio, E.W. Böhm, N. Pfeiffer, A. Gericke, Oxidative stress: a suitable therapeutic target for optic nerve diseases? Antioxidants 12 (7) (2023) 1465, https://doi.org/10.3390/antiox12071465.
[78] M. Pacurari, R. Kafoury, P.B. Tchounwou, K. Ndebele, The renin-angiotensin-aldosterone system in vascular inflammation and remodeling, Int. J. Inf. Secur. 2014 (2014) 689360, https://doi.org/10.1155/2014/689360.
[79] T. Lund, J. Vuust, R. Bravo, E. Boel, T.B. Ørstavik, K. Poulsen, In vitro studies on the conversion of the biosynthetic precursor of renin, clinical and experimental hypertension, Part A: Theory Pract. 4 (11–12) (1982) 1965–1972, https://doi.org/10.3109/10641968209062362.
[80] D.F. Catanzaro, B.J. Morris, Biosynthesis of Preprorenin. Studies using whole tissue, a cell-free system, and E. Coli containing cDna inserted at the PstI site of plasmid pBR322, clinical and experimental hypertension, Part A: Theory Pract. 4 (11–12) (1982) 1939–1963, https://doi.org/10.3109/10641968209062361.
[81] R.M. Streatfeild-James, D. Williamson, R.N. Pike, D. Tewksbury, R.W. Carrell, P. B. Coughlin, Angiotensinogen cleavage by renin: importance of a structurally constrained N-terminus, FEBS Lett. 436 (2) (1998) 267–270, https://doi.org/10.1016/s0014-5793(98)01145-4.
[82] V.J. Dzau, A. Tanaka, R.E. Pratt, The nature of renin precursor and inactive renin, clinical and experimental hypertension, Part A: Theory Pract. 4 (11–12) (1982) 1973–1985, https://doi.org/10.3109/10641968209062363.
[83] G. Yang, D.C. Merrill, M.W. Thompson, J.E. Robillard, C.D. Sigmund, Functional expression of the human angiotensinogen gene in transgenic mice, J. Biol. Chem. 269 (51) (1994) 32497–32502. https://www.ncbi.nlm.nih.gov/pubmed/7798251.
[84] A. Fukamizu, K. Sugimura, E. Takimoto, F. Sugiyama, M.S. Seo, S. Takahashi, T. Hatae, N. Kajiwara, K. Yagami, K. Murakami, Chimeric renin-angiotensin system demonstrates sustained increase in blood pressure of transgenic mice carrying both human renin and human angiotensinogen genes, J. Biol. Chem. 268 (16) (1993) 11617–11621. https://www.ncbi.nlm.nih.gov/pubmed/8505294.
[85] M. Mukoyama, M. Nakajima, M. Horiuchi, H. Sasamura, R.E. Pratt, V. Dzau, Expression cloning of type 2 angiotensin II receptor reveals a unique class of seven-transmembrane receptors, J. Biol. Chem. 268 (33) (1993) 24539–24542. https://www.ncbi.nlm.nih.gov/pubmed/8227010.
[86] A. Bonnardeaux, E. Davies, X. Jeunemaitre, I. Féry, A. Charru, E. Clauser, L. Tiret, F. Cambien, P. Corvol, F. Soubrier, Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension, Hypertension 24 (1) (1994) 63–69, https://doi.org/10.1161/01.hyp.24.1.63.
[87] T. Murphy, R.W. Alexander, K.K. Griendling, M.S. Runge, K.E. Bernstein, Isolation of a cDNA encoding the vascular type-1 angiotensin II receptor, Nature 351 (6323) (1991) 233–236, https://doi.org/10.1038/351233a0.
[88] K. Sasaki, Y. Yamano, S. Bardhan, N. Iwai, J.J. Murray, M. Hasegawa, Y. Matsudat, T. Lnagami, Cloning and expression of a complementary DNA encoding a bovine adrenal angiotensin II type-1 receptor, Nature 351 (6323) (1991) 230–233, https://doi.org/10.1038/351230a0.
[89] B.C. Berk, M.A. Corson, Angiotensin II signal transduction in vascular smooth muscle, Circ. Res. 80 (5) (1997) 607–616, https://doi.org/10.1161/01.RES.80.5.607.
[90] I.Z. Jaffe, M.E. Mendelsohn, Angiotensin II and aldosterone regulate gene transcription via functional Mineralocortocoid receptors in human coronary artery smooth muscle cells, Circ. Res. 96 (6) (2005) 643–650, https://doi.org/10.1161/01.RES.0000159937.05502.d1.
[91] S. Patel, T. Hussain, Dimerization of AT(2) and mas receptors in control of blood pressure, Curr. Hypertens. Rep. 20 (5) (2018) 41, https://doi.org/10.1007/s11906-018-0845-3.
[92] J. Leonhardt, D.C. Villela, A. Teichmann, L.-M. Münter, M.C. Mayer, M. Mardahl, S. Kirsch, P. Namsolleck, K. Lucht, V. Benz, N. Alenina, N. Daniell, M. Horiuchi, M. Iwai, G. Multhaup, R. Schülein, M. Bader, R.A. Santos, T. Unger, U. M. Steckelings, Evidence for Heterodimerization and functional interaction of the angiotensin type 2 receptor and the receptor MAS, Hypertension 69 (6) (2017) 1128–1135, https://doi.org/10.1161/HYPERTENSIONAHA.116.08814.
[93] C. Mercure, A. Yogi, G.E. Callera, A.B. Aranha, M. Bader, A.J. Ferreira, R. A. Santos, T. Walther, R.M. Touyz, T.L. Reudelhuber, Angiotensin(1-7) blunts hypertensive cardiac remodeling by a direct effect on the heart, Circ. Res. 103 (11) (2008) 1319–1326, https://doi.org/10.1161/circresaha.108.184911.
[94] E.A. Tallant, C.M. Ferrario, P.E. Gallagher, Angiotensin-(1-7) inhibits growth of cardiac myocytes through activation of the mas receptor, Am. J. Physiol. Heart Circ. Physiol. 289 (4) (2005) H1560–H1566, https://doi.org/10.1152/ajpheart.00941.2004.
[95] W.O. Sampaio, R.A. Souza dos Santos, R. Faria-Silva, L.T. da Mata Machado, E. L. Schiffrin, R.M. Touyz, Angiotensin-(1-7) through receptor mas mediates endothelial nitric oxide synthase activation via Akt-dependent pathways, Hypertension 49 (1) (2007) 185–192, https://doi.org/10.1161/01.HYP.0000251865.35728.2f.
[96] R.A.S. Santos, A.C.S. e Silva, C. Maric, D.M.R. Silva, R.P. Machado, I. de Buhr, S. Heringer-Walther, S.V.B. Pinheiro, M.T. Lopes, M. Bader, E.P. Mendes, V. S. Lemos, M.J. Campagnole-Santos, H.-P. Schultheiss, R. Speth, T. Walther, Angiotensin-(1–7) is an endogenous ligand for the G protein-coupled receptor Mas, Proc. Natl. Acad. Sci. 100 (14) (2003) 8258–8263, https://doi.org/10.1073/pnas.1432869100.
[97] J. Lo, V.B. Patel, Z. Wang, J. Levasseur, S. Kaufman, J.M. Penninger, G.Y. Oudit, Angiotensin-converting enzyme 2 antagonizes angiotensin II-induced pressor response and NADPH oxidase activation in Wistar-Kyoto rats and spontaneously hypertensive rats, Exp. Physiol. 98 (1) (2013) 109–122, https://doi.org/10.1113/expphysiol.2012.067165.
[98] M. Donoghue, F. Hsieh, E. Baronas, K. Godbout, M. Gosselin, N. Stagliano, M. Donovan, B. Woolf, K. Robison, R. Jeyaseelan, A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9, Circ. Res. 87 (5) (2000) e1–e9, https://doi.org/10.1161/01.res.87.5.e1.
[99] G.I. Rice, D.A. Thomas, P.J. Grant, A.J. Turner, N.M. Hooper, Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism, Biochem. J. 383 (1) (2004) 45–51, https://doi.org/10.1042/BJ20040634.
[100] C. Vickers, P. Hales, V. Kaushik, L. Dick, J. Gavin, J. Tang, K. Godbout, T. Parsons, E. Baronas, F. Hsieh, Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase, J. Biol. Chem. 277 (17) (2002) 14838–14843, https://doi.org/10.1074/jbc.M200581200.
[101] A.A. Gonzalez, L.S. Lara, C. Luffman, D.M. Seth, M.C. Prieto, Soluble form of the (pro)renin receptor is augmented in the collecting duct and urine of chronic angiotensin II-dependent hypertensive rats, Hypertension 57 (4) (2011) 859–864, https://doi.org/10.1161/hypertensionaha.110.167957.
[102] Y. Amari, S. Morimoto, C. Suda, T. Iida, H. Okuda, T. Yurugi, Y. Oyama, N. Aoyama, F. Nakajima, A. Ichihara, Serum soluble (pro)renin receptor level as a prognostic factor in patients undergoing maintenance hemodialysis, Sci. Rep. 11 (1) (2021) 17402, https://doi.org/10.1038/s41598-021-96892-6.
[103] J. Wang, A. Nishiyama, M. Matsuyama, Z. Wang, Y. Yuan, The (pro)renin receptor: a novel biomarker and potential therapeutic target for various cancers, Cell Communicat. Signal. 18 (1) (2020) 39, https://doi.org/10.1186/s12964-020-0531-3.
[104] C.-M. Cruciat, B. Ohkawara, S.P. Acebron, E. Karaulanov, C. Reinhard, D. Ingelfinger, M. Boutros, C. Niehrs, Requirement of Prorenin receptor and vacuolar H+-ATPase–mediated acidification for Wnt signaling, Science 327 (5964) (2010) 459–463, https://doi.org/10.1126/science.1179802.
[105] G. Nguyen, F. Delarue, C. Burcklé, L. Bouzhir, T. Giller, J.-D. Sraer, Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin, J. Clin. Invest. 109 (11) (2002) 1417–1427, https://doi.org/10.1172/JCI14276.
[106] S. Morimoto, T. Ando, M. Niiyama, Y. Seki, N. Yoshida, D. Watanabe, F. Kawakami-Mori, H. Kobori, A. Nishiyama, A. Ichihara, Serum soluble (pro) renin receptor levels in patients with essential hypertension, Hypertens. Res. 37 (7) (2014) 642–648, https://doi.org/10.1038/hr.2014.46.
[107] A. Danser, M. Van Den Dorpel, J. Deinum, F. Derkx, A. Franken, E. Peperkamp, P. De Jong, M. Schalekamp, Renin, prorenin, and immunoreactive renin in vitreous fluid from eyes with and without diabetic retinopathy, J. Clin. Endocrinol. Metab. 68 (1) (1989) 160–167, https://doi.org/10.1210/jcem-68-1-160.
[108] S. Sramek, I. Wallow, R. Day, E. Ehrlich, Ocular renin-angiotensin: immunohistochemical evidence for the presence of prorenin in eye tissue, Invest. Ophthalmol. Vis. Sci. 29 (11) (1988) 1749–1752. https://www.ncbi.nlm.nih.gov/pubmed/3053530.
[109] I.H. Wallow, S.J. Sramek, C.D. Bindley, S.R. Darjatmoko, S.J. Gange, Ocular renin angiotensin: EM immunocytochemical localization of prorenin, Curr. Eye Res. 12 (10) (1993) 945–950, https://doi.org/10.3109/02713689309020401.
[110] J. Wagner, A.J. Danser, F. Derkx, T. De Jong, M. Paul, J.J. Mullins, M. Schalekamp, D. Ganten, Demonstration of renin mRNA, angiotensinogen mRNA, and angiotensin converting enzyme mRNA expression in the human eye: evidence for an intraocular renin-angiotensin system, Br. J. Ophthalmol. 80 (2) (1996) 159–163, https://doi.org/10.1136/bjo.80.2.159.
[111] G. Ferrari-Dileo, J. Ryan, E. Rockwood, E. Davis, D. Anderson, Angiotensin-converting enzyme in bovine, feline, and human ocular tissues, Invest. Ophthalmol. Vis. Sci. 29 (6) (1988) 876–881. https://www.ncbi.nlm.nih.gov/pubmed/2836331.
[112] V.M. Milenkovic, M. Brockmann, C. Meyer, M. Desch, F. Schweda, A. Kurtz, V. Todorov, O. Strauss, Regulation of the renin expression in the retinal pigment epithelium by systemic stimuli, American J. Physiol.-Renal Physiol. 299 (2) (2010) F396–F403, https://doi.org/10.1152/ajprenal.00576.2009.
[113] A. Vaajanen, G. Kalesnykas, H. Vapaatalo, H. Uusitalo, The expression of mas-receptor of the renin–angiotensin system in the human eye, Graefes Arch. Clin. Exp. Ophthalmol. 253 (7) (2015) 1053–1059, https://doi.org/10.1007/s00417-015-2952-z.
[114] R.P. Igic, C.J. Robinson, E.G. Erdös, Angiotensin I Converting Enzyme Activity in the Choroid Plexus and in the Retina, Central Actions of Angiotensin and Related Hormones, Elsevier, 1977, pp. 23–27, https://doi.org/10.1016/B978-0-08-020933-3.50008-8.
[115] K.M. Mirabito Colafella, D.M. Bovée, A.H.J. Danser, The renin-angiotensin-aldosterone system and its therapeutic targets, Exp. Eye Res. 186 (2019) 107680, https://doi.org/10.1016/j.exer.2019.05.020.
[116] C.R. Brandt, A.M. Pumfery, B. Micales, C.D. Bindley, G.E. Lyons, S.J. Sramek, I. H. Wallow, Renin mRNA is synthesized locally in rat ocular tissues, Curr. Eye Res. 13 (10) (1994) 755–763, https://doi.org/10.3109/02713689409047011.

[117] M. Holappa, J. Valjakka, A. Vaajanen, Angiotensin(1-7) and ACE2, "the hot spots" of renin-angiotensin system, detected in the human aqueous humor, Open Ophthalmol J 9 (2015) 28–32, https://doi.org/10.2174/1874364101509010028.
[118] C. Tikellis, C.I. Johnston, J.M. Forbes, W.C. Burns, M.C. Thomas, R.A. Lew, M. Yarski, A.I. Smith, M.E. Cooper, Identification of angiotensin converting enzyme 2 in the rodent retina, Curr. Eye Res. 29 (6) (2004) 419–427, https://doi.org/10.1080/02713680490517944.
[119] Y. Dong, A. Kanda, K. Noda, W. Saito, S. Ishida, Pathologic roles of receptor-associated Prorenin system in idiopathic Epiretinal membrane, Sci. Rep. 7 (1) (2017) 44266, https://doi.org/10.1038/srep44266.
[120] A. Kanda, K. Noda, W. Saito, S. Ishida, (pro) renin receptor is associated with angiogenic activity in proliferative diabetic retinopathy, Diabetologia 55 (2012) 3104–3113, https://doi.org/10.1007/s00125-012-2702-2.
[121] A. Kanda, K. Noda, W. Saito, S. Ishida, Vitreous renin activity correlates with vascular endothelial growth factor in proliferative diabetic retinopathy, Br. J. Ophthalmol. 97 (5) (2013) 666–668.
[122] S. Satofuka, A. Ichihara, N. Nagai, K. Noda, Y. Ozawa, A. Fukamizu, K. Tsubota, H. Itoh, Y. Oike, S. Ishida, (pro) renin receptor promotes choroidal neovascularization by activating its signal transduction and tissue renin-angiotensin system, Am. J. Pathol. 173 (6) (2008) 1911–1918, https://doi.org/10.2353/ajpath.2008.080457.
[123] S. Satofuka, A. Ichihara, N. Nagai, K. Noda, Y. Ozawa, A. Fukamizu, K. Tsubota, H. Itoh, Y. Oike, S. Ishida, (pro) renin receptor–mediated signal transduction and tissue renin-angiotensin system contribute to diabetes-induced retinal inflammation, Diabetes 58 (7) (2009) 1625–1633, https://doi.org/10.2337/db08-0254.
[124] A. Ichihara, Y. Kaneshiro, T. Takemitsu, M. Sakoda, F. Suzuki, T. Nakagawa, A. Nishiyama, T. Inagami, M. Hayashi, Nonproteolytic activation of prorenin contributes to development of cardiac fibrosis in genetic hypertension, Hypertension 47 (5) (2006) 894–900, https://doi.org/10.1161/01.HYP.0000215838.48170.0b.
[125] Y. Huang, S. Wongamorntham, J. Kasting, D. McQuillan, R. Owens, L. Yu, N. Noble, W. Border, Renin increases mesangial cell transforming growth factor-β1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms, Kidney Int. 69 (1) (2006) 105–113, https://doi.org/10.1038/sj.ki.5000011.
[126] K. Narumi, E. Sato, T. Hirose, T. Yamamoto, T. Nakamichi, M. Miyazaki, H. Sato, S. Ito, (pro) renin receptor is involved in mesangial fibrosis and matrix expansion, Sci. Rep. 8 (1) (2018) 16, https://doi.org/10.1038/s41598-017-18314-w.
[127] M. He, L. Zhang, Y. Shao, X. Wang, Y. Huang, T. Yao, L. Lu, Inhibition of renin/prorenin receptor attenuated mesangial cell proliferation and reduced associated fibrotic factor release, Eur. J. Pharmacol. 606 (1–3) (2009) 155–161, https://doi.org/10.1016/j.ejphar.2008.12.050.
[128] Z. Fu, F. Wang, X. Liu, J. Hu, J. Su, X. Lu, A. Lu, J.M. Cho, J.D. Symons, C.J. Zou, T. Yang, Soluble (pro)renin receptor induces endothelial dysfunction and hypertension in mice with diet-induced obesity via activation of angiotensin II type 1 receptor, Clin. Sci. (Lond.) 135 (6) (2021) 793–810, https://doi.org/10.1042/cs20201047.
[129] E.T. Ishizuka, A. Kanda, Y. Shinmei, T. Ohguchi, Y. Tagawa, K. Hase, T. Yamamoto, K. Noda, S. Chin, S. Ishida, Receptor-associated Prorenin system in the trabecular meshwork of patients with primary open-angle Glaucoma and Neovascular Glaucoma, J. Clin. Med. 9 (8) (2020) 2336, https://doi.org/10.3390/jcm9082336.
[130] R. Barro-Soria, J. Stindl, C. Müller, R. Foeckler, V. Todorov, H. Castrop, O. Strauß, Angiotensin-2-mediated Ca2+ signaling in the retinal pigment epithelium: role of angiotensin-receptor-associated-protein and TRPV2 channel, PLoS One 7 (11) (2012) e49624, https://doi.org/10.1371/journal.pone.0049624.
[131] S.K. Fellner, W.J. Arendshorst, Angiotensin II Ca2+ signaling in rat afferent arterioles: stimulation of cyclic ADP ribose and IP3 pathways, American J. Physiol.-Renal Physiol. 288 (4) (2005) F785–F791, https://doi.org/10.1152/ajprenal.00372.2004.
[132] I. Harman-Boehm, T. Sosna, H. Lund-Andersen, M. Porta, The eyes in diabetes and diabetes through the eyes, Diabetes Res. Clin. Pract. 78 (3) (2007) S51–S58, https://doi.org/10.1016/j.diabres.2007.09.023.
[133] R.E. Gilbert, D. Kelly, A.J. Cox, J. Wilkinson-Berka, J. Rumble, T. Osicka, S. Panagiotopoulos, V. Lee, E. Hendrich, G. Jerums, Angiotensin converting enzyme inhibition reduces retinal overexpression of vascular endothelial growth factor and hyperpermeability in experimental diabetes, Diabetologia 43 (11) (2000) 1360–1367, https://doi.org/10.1007/s001250051539.
[134] Y. Nagisa, A. Shintani, S. Nakagawa, The angiotensin II receptor antagonist candesartan cilexetil (TCV-116) ameliorates retinal disorders in rats, Diabetologia 44 (7) (2001) 883–888, https://doi.org/10.1007/s001250100556.
[135] M. Pons, S.W. Cousins, O. Alcazar, G.E. Striker, M.E. Marin-Castaño, Angiotensin II–induced MMP-2 activity and MMP-14 and basigin protein expression are mediated via the angiotensin II receptor type 1–mitogen-activated protein kinase 1 pathway in retinal pigment epithelium: implications for age-related macular degeneration, Am. J. Pathol. 178 (6) (2011) 2665–2681, https://doi.org/10.1016/j.ajpath.2011.02.006.
[136] N. Nagai, K. Izumi-Nagai, Y. Oike, T. Koto, S. Satofuka, Y. Ozawa, K. Yamashiro, M. Inoue, K. Tsubota, K. Umezawa, Suppression of diabetes-induced retinal inflammation by blocking the angiotensin II type 1 receptor or its downstream nuclear factor-κB pathway, Invest. Ophthalmol. Vis. Sci. 48 (9) (2007) 4342–4350, https://doi.org/10.1167/iovs.06-1473.
[137] M.S. Ola, M.M. Ahmed, H.M. Abuohashish, S.S. Al-Rejaie, A.S. Alhomida, Telmisartan ameliorates neurotrophic support and oxidative stress in the retina of streptozotocin-induced diabetic rats, Neurochem. Res. 38 (8) (2013) 1572–1579, https://doi.org/10.1007/s11064-013-1058-4.
[138] M.C. Zimmerman, E. Lazartigues, J.A. Lang, P. Sinnayah, I.M. Ahmad, D.R. Spitz, R.L. Davisson, Superoxide mediates the actions of angiotensin II in the central nervous system, Circ. Res. 91 (11) (2002) 1038–1045, https://doi.org/10.1161/01.RES.0000043501.47934.FA.
[139] J.L. Wilkinson-Berka, I. Rana, R. Armani, A. Agrotis, Reactive oxygen species, Nox and angiotensin II in angiogenesis: implications for retinopathy, Clin. Sci. 124 (10) (2013) 597–615.
[140] K.K. Griendling, C.A. Minieri, J.D. Ollerenshaw, R.W. Alexander, Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells, Circ. Res. 74 (6) (1994) 1141–1148.
[141] G. Wang, C.G. Coleman, M.J. Glass, P. Zhou, Q. Yu, L. Park, J. Anrather, V. M. Pickel, C. Iadecola, Angiotensin II type 2 receptor-coupled nitric oxide production modulates free radical availability and voltage-gated Ca2+ currents in NTS neurons, Am. J. Phys. Regul. Integr. Comp. Phys. 302 (9) (2012) R1076–R1083, https://doi.org/10.1152/ajpregu.00571.2011.
[142] M.-O. Guimond, N. Gallo-Payet, How does angiotensin AT2 receptor activation help neuronal differentiation and improve neuronal pathological situations? Front. Endocrinol. 3 (2012) 164, https://doi.org/10.3389/fendo.2012.00164.
[143] J.H. Lee, S. Xia, L. Ragolia, Upregulation of AT2 receptor and iNOS impairs angiotensin II-induced contraction without endothelium influence in young normotensive diabetic rats, Am. J. Phys. Regul. Integr. Comp. Phys. 295 (1) (2008) R144–R154.
[144] A. Verma, P. Zhu, A. de Kloet, E. Krause, C. Sumners, Q. Li, Angiotensin receptor expression revealed by reporter mice and beneficial effects of AT2R agonist in retinal cells, Exp. Eye Res. 187 (2019) 107770, https://doi.org/10.1016/j.exer.2019.107770.
[145] L. Mateos, M.J. Perez-Alvarez, F. Wandosell, Angiotensin II type-2 receptor stimulation induces neuronal VEGF synthesis after cerebral ischemia, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1862 (7) (2016) 1297–1308, https://doi.org/10.1016/j.bbadis.2016.03.013.
[146] D. Young, G. Waitches, C. Birchmeier, O. Fasano, M. Wigler, Isolation and characterization of a new cellular oncogene encoding a protein with multiple potential transmembrane domains, Cell 45 (5) (1986) 711–719, https://doi.org/10.1016/0092-8674(86)90785-3.
[147] C.M. Ferrario, S.N. Iyer, Angiotensin-(1–7): a bioactive fragment of the renin–angiotensin system, Regul. Pept. 78 (1–3) (1998) 13–18, https://doi.org/10.1016/s0167-0115(98)00134-7.
[148] A.Z. El-Hashim, W.M. Renno, R. Raghupathy, H.T. Abduo, S. Akhtar, I.F. Benter, Angiotensin-(1-7) inhibits allergic inflammation, via the MAS1 receptor, through suppression of ERK1/2- and NF-κB-dependent pathways, Br. J. Pharmacol. 166 (6) (2012) 1964–1976, https://doi.org/10.1111/j.1476-5381.2012.01905.x.
[149] V. Burghi, E.B. Echeverría, M.H. Sosa, D.T. Quiroga, M.C. Muñoz, C. Davio, F. Monczor, N.C. Fernández, F.P. Dominici, Participation of Gαi-adenylate cyclase and ERK1/2 in mas receptor signaling pathways, Front. Pharmacol. 10 (2019) 146, https://doi.org/10.3389/fphar.2019.00146.
[150] V. Burghi, E.B. Echeverría, M.H. Sosa, D.T. Quiroga, M.C. Muñoz, C. Davio, F. Monczor, N.C. Fernández, F.P. Dominici, Participation of Gα(i)-adenylate cyclase and ERK1/2 in mas receptor signaling pathways, Front. Pharmacol. 10 (2019) 146, https://doi.org/10.3389/fphar.2019.00146.
[151] W. Zeng, W. Chen, X. Leng, J.G. He, H. Ma, Chronic angiotensin-(1-7) administration improves vascular remodeling after angioplasty through the regulation of the TGF-beta/Smad signaling pathway in rabbits, Biochem. Biophys. Res. Commun. 389 (1) (2009) 138–144, https://doi.org/10.1016/j.bbrc.2009.08.112.
[152] Y.-T. Lin, H.-C. Wang, H.-C. Chuang, Y.-C. Hsu, M.-Y. Yang, C.-Y. Chien, Pre-treatment with angiotensin-(1–7) inhibits tumor growth via autophagy by downregulating PI3K/Akt/mTOR signaling in human nasopharyngeal carcinoma xenografts, J. Mol. Med. 96 (12) (2018) 1407–1418, https://doi.org/10.1007/s00109-018-1704-z.
[153] A. Vaajanen, H. Vapaatalo, H. Kautiainen, O. Oksala, Angiotensin (1-7) reduces intraocular pressure in the normotensive rabbit eye, Invest. Ophthalmol. Vis. Sci. 49 (6) (2008) 2557–2562, https://doi.org/10.1167/iovs.07-1399.
[154] P.J. Fuller, Y.-Z. Yao, R. Jin, S. He, B. Martín-Fernández, M.J. Young, B.J. Smith, Molecular evolution of the switch for progesterone and spironolactone from mineralocorticoid receptor agonist to antagonist, Proc. Natl. Acad. Sci. 116 (37) (2019) 18578–18583, https://doi.org/10.1073/pnas.1903172116.
[155] S. Green, P. Chambon, Oestradiol induction of a glucocorticoid-responsive gene by a chimaeric receptor, Nature 325 (6099) (1987) 75–78, https://doi.org/10.1038/325075a0.
[156] M. Zhao, F. Valamanesh, I. Celerier, M. Savoldelli, L. Jonet, J.C. Jeanny, F. Jaisser, N. Farman, F. Behar-Cohen, The neuroretina is a novel mineralocorticoid target: aldosterone up-regulates ion and water channels in Müller glial cells, FASEB J. 24 (9) (2010) 3405–3415, https://doi.org/10.1096/fj.09-154344.
[157] M. Zhao, I. Célérier, E. Bousquet, J.-C. Jeanny, L. Jonet, M. Savoldelli, O. Offret, A. Curan, N. Farman, F. Jaisser, Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy, J. Clin. Invest. 122 (7) (2012) 2672–2679, https://doi.org/10.1172/JCI61427.
[158] M. Caprio, B.G. Newfell, A. La Sala, W. Baur, A. Fabbri, G. Rosano, M. E. Mendelsohn, I.Z. Jaffe, Functional mineralocorticoid receptors in human vascular endothelial cells regulate intercellular adhesion molecule-1 expression and promote leukocyte adhesion, Circ. Res. 102 (11) (2008) 1359–1367, https://doi.org/10.1161/CIRCRESAHA.108.174235.

[159] G. Jia, J. Habibi, A.R. Aroor, L.A. Martinez-Lemus, V.G. DeMarco, F.I. Ramirez-Perez, Z. Sun, M.R. Hayden, G.A. Meininger, K.B. Mueller, Endothelial mineralocorticoid receptor mediates diet-induced aortic stiffness in females, Circ. Res. 118 (6) (2016) 935–943, https://doi.org/10.1161/CIRCRESAHA.115.308269.
[160] D. Deliyanti, A.G. Miller, G. Tan, K.J. Binger, A.L. Samson, J.L. Wilkinson-Berka, Neovascularization is attenuated with aldosterone synthase inhibition in rats with retinopathy, Hypertension 59 (3) (2012) 607–613.
[161] J.L. Wilkinson-Berka, G. Tan, K. Jaworski, J. Harbig, A.G. Miller, Identification of a retinal aldosterone system and the protective effects of mineralocorticoid receptor antagonism on retinal vascular pathology, Circ. Res. 104 (1) (2009) 124–133.
[162] G. Leung, A. Grant, A.N. Garas, G. Li, E.E. Freeman, A systematic review and Meta-analysis of systemic antihypertensive medications with intraocular pressure and Glaucoma, Am. J. Ophthalmol. 255 (2023) 7–17, https://doi.org/10.1016/j.ajo.2023.03.014.
[163] J.S. Lee, H.R. Cha, H.W. Bae, S.Y. Lee, W. Choi, S.W. Lee, C.Y. Kim, Effect of antihypertensive medications on the risk of open-angle glaucoma, Sci. Rep. 13 (1) (2023) 16224, https://doi.org/10.1038/s41598-023-43420-3.
[164] A. Vaajanen, Expression and Function of Angiotensins in the Regulation of Intraocular Pressure-an Experimental Study, 2009.
[165] C. Lin, R.A. Stone, M. Wax, Angiotensin binding sites in rabbit anterior uvea and human ciliary epithelial cells, Invest. Ophthalmol. Vis. Sci. 31 (1) (1990) 147–152. https://www.ncbi.nlm.nih.gov/pubmed/2298535.
[166] A. Cullinane, P. Leung, J. Ortego, M. Coca-Prados, B. Harvey, Renin-angiotensin system expression and secretory function in cultured human ciliary body non-pigmented epithelium, Br. J. Ophthalmol. 86 (6) (2002) 676–683, https://doi.org/10.1136/bjo.86.6.676.
[167] C. Gerhardinger, M.B.S. Costa, M.C. Coulombe, I. Toth, T. Hoehn, P. Grosu, Expression of acute-phase response proteins in retinal Müller cells in diabetes, Invest. Ophthalmol. Vis. Sci. 46 (1) (2005) 349–357, https://doi.org/10.1167/iovs.04-0860.
[168] E.L. Fletcher, J.A. Phipps, M.M. Ward, K.A. Vessey, J.L. Wilkinson-Berka, The renin–angiotensin system in retinal health and disease: its influence on neurons, glia and the vasculature, Prog. Retin. Eye Res. 29 (4) (2010) 284–311, https://doi.org/10.1016/j.preteyeres.2010.03.003.
[169] J.A. Phipps, K.A. Vessey, A. Brandli, N. Nag, M.X. Tran, A.I. Jobling, E.L. Fletcher, The role of angiotensin II/AT1 receptor signaling in regulating retinal microglial activation, Invest. Ophthalmol. Vis. Sci. 59 (1) (2018) 487–498, https://doi.org/10.1167/iovs.17-22416.
[170] A. Clermont, S.-E. Bursell, E.P. Feener, Role of the angiotensin II type 1 receptor in the pathogenesis of diabetic retinopathy: effects of blood pressure control and beyond, J. Hypertens. 24 (1) (2006) S73–S80, https://doi.org/10.1097/01.hjh.0000220410.69116.f8.
[171] R.-F. Wang, S.M. Podos, T.W. Mittag, T. Yokoyoma, Effect of CS-088, an angiotensin AT1 receptor antagonist, on intraocular pressure in glaucomatous monkey eyes, Exp. Eye Res. 80 (5) (2005) 629–632, https://doi.org/10.1016/j.exer.2004.11.012.
[172] C. Costagliola, M. Verolino, M. Leonarda De Rosa, G. Iaccarino, M. Ciancaglini, L. Mastropasqua, Effect of Oral losartan potassium administration on intraocular pressure in normotensive and glaucomatous human subjects, Exp. Eye Res. 71 (2) (2000) 167–171, https://doi.org/10.1006/exer.2000.0866.
[173] C. Costagliola, R. Di Benedetto, L. De Caprio, R. Verde, L. Mastropasqua, Effect of oral captopril (SQ 14225) on intraocular pressure in man, Eur. J. Ophthalmol. 5 (1) (1995) 19–25, https://doi.org/10.1177/112067219500500104.
[174] V.J. Lotti, N. Pawlowski, Prostaglandins mediate the ocular hypotensive action of the angiotensin converting enzyme inhibitor MK-422 (Enalaprilat) in African Green monkeys, J. Ocul. Pharmacol. Ther. 6 (1) (1990) 1–7, https://doi.org/10.1089/jop.1990.6.1.
[175] R. Agarwal, A.V. Krasilnikova, I.S. Raja, P. Agarwal, N. Mohd Ismail, Mechanisms of angiotensin converting enzyme inhibitor-induced IOP reduction in normotensive rats, Eur. J. Pharmacol. 730 (2014) 8–13, https://doi.org/10.1016/j.ejphar.2014.02.021.
[176] G.B. Shah, S. Sharma, A.A. Mehta, R.K. Goyal, Oculohypotensive effect of angiotensin-converting enzyme inhibitors in acute and chronic models of Glaucoma, J. Cardiovasc. Pharmacol. 36 (2) (2000) 169–175, https://doi.org/10.1097/00005344-200008000-00005.
[177] A. Mehta, L. Iyer, S. Parmar, G. Shah, R. Goyal, Oculohypotensive effect of perindopril in acute and chronic models of glaucoma in rabbits, Can. J. Physiol. Pharmacol. 88 (5) (2010) 595–600, https://doi.org/10.1139/Y10-026.
[178] R. Osusky, J. Nussberger, C. Amstutz, J. Flammer, H.R. Brunner, Individual measurements of angiotensin II concentrations in aqueous humor of the eye, Eur. J. Ophthalmol. 4 (4) (1994) 228–233, https://doi.org/10.1177/112067219400400407.
[179] H.A. Reitsamer, J.W. Kiel, Relationship between ciliary blood flow and aqueous production in rabbits, Invest. Ophthalmol. Vis. Sci. 44 (9) (2003) 3967–3971, https://doi.org/10.1167/iovs.03-0088.
[180] H. Yang, K. Hirooka, K. Fukuda, F. Shiraga, Neuroprotective effects of angiotensin II type 1 receptor blocker in a rat model of chronic Glaucoma, Invest. Ophthalmol. Vis. Sci. 50 (12) (2009) 5800–5804, https://doi.org/10.1167/iovs.09-3678.
[181] E. Kostenis, G. Milligan, A. Christopoulos, C.F. Sanchez-Ferrer, S. Heringer-Walther, P.M. Sexton, F. Gembardt, E. Kellett, L. Martini, P. Vanderheyden, H. P. Schultheiss, T. Walther, G-protein-coupled receptor mas is a physiological antagonist of the angiotensin II type 1 receptor, Circulation 111 (14) (2005) 1806–1813, https://doi.org/10.1161/01.Cir.0000160867.23556.7d.
[182] A. Vaajanen, G. Kalesnykas, H. Vapaatalo, H. Uusitalo, The expression of mas-receptor of the renin-angiotensin system in the human eye, Graefes Arch. Clin. Exp. Ophthalmol. 253 (7) (2015) 1053–1059, https://doi.org/10.1007/s00417-015-2952-z.
[183] N.A. Sharif, Novel potential treatment modalities for ocular hypertension: focus on angiotensin and bradykinin system axes, J. Ocul. Pharmacol. Ther. 31 (3) (2015) 131–145, https://doi.org/10.1089/jop.2014.0114.
[184] H. Li, H. Cui, J. Ren, D. Wang, R. Zhao, S. Zhu, S. Liu, X. Liu, S. Tian, Y. Zhang, P. Zhao, P. Li, R.F. Thorne, S. Duan, Elevated angiotensin-II levels contribute to the pathogenesis of open-angle Glaucoma via inducing the expression of fibrosis-related genes in trabecular meshwork cells through a ROS/NOX4/SMAD3 Axis, Cell Transplant. 32 (2023), https://doi.org/10.1177/09636897231162526, 9636897231162526.
[185] D. Kim, U. Pattamatta, E. Kelly, P.R. Healey, N. Carnt, H. Zoellner, A.J.R. White, Inhibitory effects of angiotensin II receptor blockade on human Tenon fibroblast migration and reactive oxygen species production in cell culture, Transl. Vis. Sci. Technol. 7 (2) (2018) 20, https://doi.org/10.1167/tvst.7.2.20.
[186] D. Shi, J. Yang, Y. Jiang, L. Wen, Z. Wang, B. Yang, The antioxidant activity and neuroprotective mechanism of isoliquiritigenin, Free Radic. Biol. Med. 152 (2020) 207–215, https://doi.org/10.1016/j.freeradbiomed.2020.03.016.
[187] H. Ye, X. Yang, X. Chen, L. Shen, R. Le, Isoliquiritigenin protects against angiotensin II-induced fibrogenesis by inhibiting NF-κB/PPARγ inflammatory pathway in human Tenon's capsule fibroblasts, Exp. Eye Res. 199 (2020) 108146, https://doi.org/10.1016/j.exer.2020.108146.
[188] H. Shi, Y. Zhang, S. Fu, Z. Lu, W. Ye, Y. Xiao, Angiotensin II as a Morphogenic cytokine stimulating Fibrogenesis of human Tenon's capsule fibroblasts, Invest. Ophthalmol. Vis. Sci. 56 (2) (2015) 855–864, https://doi.org/10.1167/iovs.14-15301.
[189] Y. Liu, A. Kanda, D. Wu, E.T. Ishizuka, S. Kase, K. Noda, A. Ichihara, S. Ishida, Suppression of choroidal neovascularization and fibrosis by a novel RNAi therapeutic agent against (pro)renin receptor, Mol. Therapy - Nucleic Acids 17 (2019) 113–125, https://doi.org/10.1016/j.omtn.2019.05.012.
[190] A. Kanda, E.T. Ishizuka, A. Shibata, T. Matsumoto, H. Toyofuku, K. Noda, K. Namba, S. Ishida, A novel single-Strand RNAi therapeutic agent targeting the (pro)renin receptor suppresses ocular inflammation, Mol. Therapy - Nucleic Acids 7 (2017) 116–126, https://doi.org/10.1016/j.omtn.2017.01.001.
[191] Q. Li, P.K. Shil, A. Verma, P. Zhu, J.A. Danser, W.W. Batenburg, Suppression of ocular inflammation by a combination of renin inhibitor and prorenin receptor blocker, Invest. Ophthalmol. Vis. Sci. 55 (13) (2014) 6295.
[192] K. Hase, A. Kanda, I. Hirose, K. Noda, S. Ishida, Systemic factors related to soluble (pro)renin receptor in plasma of patients with proliferative diabetic retinopathy, PLoS One 12 (12) (2017) e0189696, https://doi.org/10.1371/journal.pone.0189696.
[193] A. Kanda, S. Ishida, Receptor-associated prorenin system contributes to development of inflammation and angiogenesis in proliferative diabetic retinopathy, Inflammat. Regenerat. 36 (1) (2016) 22, https://doi.org/10.1186/s41232-016-0027-0.
[194] A. Verma, Y. Wang, P. Zhu, P.K. Shil, T. Prasad, Q. Li, Role of Prorenin and Prorenin receptor in ocular inflammation, Invest. Ophthalmol. Vis. Sci. 55 (13) (2014) 2191.
[195] J.L. Wilkinson-Berka, Prorenin and the (pro)renin receptor in ocular pathology, Am. J. Pathol. 173 (6) (2008) 1591–1594, https://doi.org/10.2353/ajpath.2008.080757.
[196] S. Satofuka, A. Ichihara, N. Nagai, K. Yamashiro, T. Koto, H. Shinoda, K. Noda, Y. Ozawa, M. Inoue, K. Tsubota, F. Suzuki, Y. Oike, S. Ishida, Suppression of ocular inflammation in endotoxin-induced uveitis by inhibiting nonproteolytic activation of Prorenin, Invest. Ophthalmol. Vis. Sci. 47 (6) (2006) 2686–2692, https://doi.org/10.1167/iovs.05-1458.
[197] S. Satofuka, A. Ichihara, N. Nagai, T. Koto, H. Shinoda, K. Noda, Y. Ozawa, M. Inoue, K. Tsubota, H. Itoh, Y. Oike, S. Ishida, Role of Nonproteolytically activated Prorenin in pathologic, but not physiologic, retinal neovascularization, Invest. Ophthalmol. Vis. Sci. 48 (1) (2007) 422–429, https://doi.org/10.1167/iovs.06-0534.
[198] K.B. Biswas, A. Nabi, Y. Arai, T. Nakagawa, A. Ebihara, A. Ichihara, T. Watanabe, T. Inagami, F. Suzuki, Aliskiren binds to renin and prorenin bound to (pro) renin receptor in vitro, Hypertens. Res. 33 (10) (2010) 1053–1059, https://doi.org/10.1038/hr.2010.136.
[199] Y. Ozawa, K. Yuki, R. Yamagishi, K. Tsubota, M. Aihara, Renin–angiotensin system involvement in the oxidative stress-induced neurodegeneration of cultured retinal ganglion cells, Jpn. J. Ophthalmol. 57 (1) (2013) 126–132, https://doi.org/10.1007/s10384-012-0204-x.
[200] K. Asraf, N. Torika, R.N. Apte, S. Fleisher-Berkovich, Microglial activation is modulated by captopril: in vitro and in vivo studies, Front. Cell. Neurosci. 12 (2018) 116, https://doi.org/10.3389/fncel.2018.00116.
[201] S.A. Bhat, R. Goel, S. Shukla, R. Shukla, K. Hanif, Angiotensin receptor blockade by inhibiting glial activation promotes hippocampal neurogenesis via activation of Wnt/β-catenin signaling in hypertension, Mol. Neurobiol. 55 (6) (2018) 5282–5298, https://doi.org/10.1007/s12035-017-0754-5.
[202] K. Semba, K. Namekata, X. Guo, C. Harada, T. Harada, Y. Mitamura, Renin–angiotensin system regulates neurodegeneration in a mouse model of normal tension glaucoma, Cell Death Dis. 5 (7) (2014) e1333, https://doi.org/10.1038/cddis.2014.296.
[203] S.J. Jeon, H.B. Hwang, N.Y. Lee, Evaluation of systemic renin and angiotensin II levels in Normal tension Glaucoma, J. Clin. Med. 9 (12) (2020) 3838, https://doi.org/10.3390/jcm9123838.

[204] S.-E. Oh, J.-H. Kim, H.-J. Shin, S.-A. Kim, C.-K. Park, H.-Y.L. Park, Angiotensin II-related activation of scleral fibroblasts and their role on retinal ganglion cell death in Glaucoma, Pharmaceuticals 16 (4) (2023) 556, https://doi.org/10.3390/ph16040556.

[205] M. Zhao, I. Mantel, E. Gelize, X. Li, X. Xie, A. Arboleda, M. Seminel, R. Levy-Boukris, M. Dernigoghossian, A. Prunotto, Mineralocorticoid receptor antagonism limits experimental choroidal neovascularization and structural changes associated with neovascular age-related macular degeneration, Nat. Commun. 10 (1) (2019) 369, https://doi.org/10.1038/s41467-018-08125-6.

[206] E. Nitta, K. Hirooka, K. Tenkumo, T. Fujita, A. Nishiyama, T. Nakamura, T. Itano, F. Shiraga, Aldosterone: a mediator of retinal ganglion cell death and the potential role in the pathogenesis in normal-tension glaucoma, Cell Death Dis. 4 (7) (2013) e711, https://doi.org/10.1038/cddis.2013.240.

[207] Y. Takasago, K. Hirooka, Y. Nakano, M. Kobayashi, A. Ono, Elevated plasma aldosterone levels are associated with a reduction in retinal ganglion cell survival, J. Renin-Angiotensin-Aldosterone Syst. 19 (3) (2018), https://doi.org/10.1177/1470320318795001, 1470320318795001.

[208] Y. Wada, T. Higashide, K. Sakaguchi, A. Nagata, K. Hirooka, K. Sugiyama, Compromised blood flow in the optic nerve head after systemic Administration of Aldosterone in rats: a possible rat model of retinal ganglion cell loss, Curr. Eye Res. 47 (5) (2022) 777–785, https://doi.org/10.1080/02713683.2022.2029907.

[209] K. Hirooka, Y. Kiuchi, The retinal renin-angiotensin-aldosterone system: implications for Glaucoma, Antioxidants 11 (4) (2022) 610, https://doi.org/10.3390/antiox11040610.

[210] Y. Ohshima, T. Higashide, K. Sakaguchi, M. Sasaki, S. Udagawa, S. Ohkubo, T. Yoneda, K. Sugiyama, The association of primary aldosteronism with glaucoma-related fundus abnormalities, PLoS One 15 (11) (2020) e0242090, https://doi.org/10.1371/journal.pone.0242090.

[211] A. Ono, K. Hirooka, Y. Nakano, E. Nitta, A. Nishiyama, A. Tsujikawa, Gene expression changes in the retina after systemic administration of aldosterone, Jpn. J. Ophthalmol. 62 (4) (2018) 499–507, https://doi.org/10.1007/s10384-018-0595-4.

[212] P. Rossing, J.G. Garweg, S.D. Anker, T. Osonoi, B. Pitt, S.E. Rosas, L.M. Ruilope, D. Zhu, M. Brinker, D. Finis, S. Leal, T. Schmelter, G. Bakris, Effect of finerenone on the occurrence of vision-threatening complications in patients with non-proliferative diabetic retinopathy: pooled analysis of two studies using routine ophthalmological examinations from clinical trial participants (ReFineDR/DeFineDR), Diabetes Obes. Metab. 25 (3) (2023) 894–898, https://doi.org/10.1111/dom.14915.

[213] A. Lotery, S. Sivaprasad, A. O'Connell, R.A. Harris, L. Culliford, L. Ellis, A. Cree, S. Madhusudhan, F. Behar-Cohen, U. Chakravarthy, T. Peto, C.A. Rogers, B. C. Reeves, Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): a randomised, double-blind, placebo-controlled trial, Lancet 395 (10220) (2020) 294–303, https://doi.org/10.1016/s0140-6736(19)32981-2.

[214] S.R. Sadda, Lack of efficacy of eplerenone for treatment of active central serous chorioretinopathy, Eye 34 (9) (2020) 1489–1490, https://doi.org/10.1038/s41433-020-0802-7.

[215] S.M. Sadat Razavi, R. Daneshvar, Possible dose-dependent effect of eplerenone on intraocular pressure, Indian J. Ophthalmol. 71 (10) (2023) 3357–3360, https://doi.org/10.4103/ijo.Ijo_175_23.