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Review

Therapeutic targets of renin-angiotensin system in ocular disorders

Rajesh Choudhary, Mandeep Singh Kapoor, Amrita Singh, Surendra H. Bodakhe*

Department of Pharmacology, Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur Chhattisgarh, India

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Abstract

Purpose: To review current literature on the renin-angiotensin system (RAS)-mediated pathogenic mechanisms and therapeutic targets in ocular diseases.

Methods: A comprehensive literature survey was performed on PubMed, Scopus, and Google Scholar databases published from 1977 to 2016. The search terms were a RAS, angiotensin, angiotensin receptor, prorenin, pro (renin) receptor, angiotensin converting enzyme inhibitor, angiotensin receptor blocker associated with ocular disorders like cataract, glaucoma, diabetic retinopathy (DR), macular degeneration, and uveitis. Articles were reviewed on the basis of the association between ocular disorders and RAS and relevant articles were discussed.

Results: The literature revealed that the individual RAS components including renin, angiotensins, angiotensin converting enzymes, and RAS receptors have been expressed in the specific ocular tissues like retina, choroid, and ciliary body. The activation of both circulatory and local RAS potentiate the various inflammatory and angiogenic signaling molecules, including vascular endothelial growth factor (VEGF), extracellular signal-regulated kinase, and advanced glycation end products (AGE) in the ocular tissues and leads to several blinding disorders like DR, glaucoma, and macular degeneration. The classical and newer RAS inhibitors have illustrated protective effects on blinding disorders, including DR, glaucoma, macular degeneration, uveitis, and cataract.

Conclusions: The RAS components are present in the extrarenal tissues including ocular tissue and have an imperative role in the ocular pathophysiology. The clinical studies are needed to show the role of therapeutic modalities targeting RAS in the treatment of different ocular disorders.

Keywords: Ocular renin-angiotensin system; Ocular disorders; Angiotensin II; Angiotensin II type 1 receptor; (Pro) renin receptor

Introduction

The circulatory renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, fluid volume, electrolyte balance, and inflammation.[1] The circulatory RAS system initiates with renin which cleaves angiotensinogen to form the decapeptide angiotensin I (Ang-I) is then converted to octapeptide angiotensin II (Ang-II) by the angiotensin-converting enzyme (ACE).[2] Ang-II regulates various biological effects through the activation of Angiotensin II type I receptors (AT_1R) and Angiotensin II type 2 receptors (AT_2R). Ang-II elicits most of its well-known biological effects, including vasoconstriction, electrolyte homeostasis, fibrosis, inflammation, and proliferation through activation of AT_1R.[3–5] The actions of the AT_2R are not so much defined, but they possibly oppose the actions of the AT_1R like vasodilatory effects.[6] However, findings indicate that AT_2R acts similar to AT_1R, like promoting cell growth, apoptosis, and angiogenesis in some tissues.[7–9]

Plethora researchers highlighted the significance of the local RAS in various extrarenal tissues, including the adrenal glands,[10] thymus,[11] and ocular tissues.[12] The presence and

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* Corresponding author.
E-mail address: drbodakhe@gmail.com (S.H. Bodakhe).

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functional role of the RAS components, including prorenin, renin, ACE, angiotensinogen, Ang-II, (pro)renin receptor ((P)RR), and AT_1R in the eye have been established in the several species (Table 1). These findings propose that the local RAS plays an important role in the regulation of the ocular physiology. The aim of our present article is to review the role of the RAS in the regulation of various ocular disorders such as diabetic retinopathy (DR), glaucoma, age-related macular degeneration (AMD), uveitis, and cataract, and beneficial effects of RAS regulation through RAS inhibitors in the therapeutic management of such ocular disorders.

Methods

This narrative review was based on a literature search using PubMed, Scopus, and Google Scholar databases from 1977 to 2016. The search terms were a RAS, angiotensin, angiotensin receptor, prorenin, (P)RR, angiotensin converting enzyme inhibitor, angiotensin receptor blocker associated with ocular disorders like cataract, glaucoma, DR, macular degeneration, and uveitis. All article types, including original research articles, reviews, and case reports that described the role of RAS in ocular disorders were selected and reviewed thoroughly by the authors to review RAS-mediated pathogenic mechanisms and therapeutic targets in ocular diseases.

Results

During the literature survey, 180 articles were retrieved from the databases. 148 articles were found relevant to the discussion in the present review. After extensively examining the plethora of literature on the various aspects of ocular RAS, expected to have a pivotal role in the treatment of various

Table 1
Distribution of renin-angiotensin system (RAS) components in ocular tissues in different species.

RAS components	Localization	Species	References
Prorenin	Retina, vitreous fluids, iris, ciliary body, choroid, sclera, cornea, conjunctiva	Human	2,13−15
Renin	Retina (Muller cells, RPE), iris, vitreous fluid, choroid	Human, rabbit	2,13,16−20
	Ciliary body	Human, rabbit, rat	
	Sclera, cornea	Human	
	Aqueous fluid	Rabbit	
Angiotensinogen	Retina (Muller cells, RPE), ciliary body, vitreous fluid, choroid, iris	Human, rabbit	2,19,20
	Sclera, cornea, conjunctiva	Human	
	Aqueous fluid	Rabbit	
Ang-I	Retina, choroid, subretinal fluid	Porcin	13,21
	Aqueous fluid	Human	
	Vitreous fluid	Human, porcine	
Ang-II	Retina (Muller cells, retinal vessel endothelial cells, ganglion cells, photoreceptor cells, subretinal fluid), vitreous fluid, choroid	Human, rabbit, porcine	19,21−24
	Ciliary body, aqueous fluid	Human, rabbit	
	Cornea	Human	
	Iris	Rabbit	
Ang (1−7)	Retinal Muller cells, aqueous humor	Human	24,25
ACE	Retina (Muller cells, ganglion cells, retinal vessel endothelial cells, photoreceptor cells), choroid	Human, monkey, dog, rabbit, porcine	2,19,20,23,25−39
	Ciliary body	Human, rabbit, rat, porcine	
	Aqueous fluid	Human, monkey, dog, rabbit	
	Vitreous fluid	Monkey, dog, rabbit	
	Tear fluid	Human, rabbit	
	Cornea, conjunctiva	Human	
	Iris	Human, rabbit, porcine	
	Sclera	Human, monkey, dog	
ACE2	Retina	Human, rodent, porcine	24,25,40,41
Chymase	Vitreous fluid	Human	32
(P)RR	Retina (Muller cells, RPE, ganglion cells), choroid, iris, ciliary body, cornea, conjunctiva	Human	2,42−44
AT_1R	Retina (Muller cells, amacrine cells, RPE, blood vessels, photoreceptors, ganglion cells), choroid, cornea, ciliary body, iris, conjunctiva	Human	2,18,23,24,45−48
AT_2R	Retina (Muller cells, nuclei of some inner nuclear layer neurons, and ganglion cell nuclei)	Human	9,24
Mas receptor	Retina, ciliary body	Human, Rabbit, rats	49−51

ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme type 2; Ang (1−7): angiotensin (1−7); Ang-I: angiotensin I; Ang-II: angiotensin II; AT_1R: angiotensin II type 1 receptor; AT_2R: angiotensin II type 2 receptor; (P)RR: (pro)renin receptor; RAS: renin-angiotensin system.

ocular disorders, we reviewed the essentiality of the ocular RAS system along with its role in ocular disorders.

Expression of renin-angiotensin system (RAS) components in the eye

Ocular RAS has been the focus of growing interest in the recent year after finding the RAS components in the ocular tissues. The literature concerning that research on the ocular RAS started with a study by Igic and coworkers on the detection of ACE activity in retinal homogenates.[52] Thereafter, RAS components in the eye have been established in various research studies (Table 1).

In early studies, RAS components were found in the eye but there was a lake to identify the origin of the ocular RAS, either local production or selective uptake by ocular tissues from the circulatory RAS.[13,14,52] This question has been refused after findings of Danser et al that the circulatory RAS components, including angiotensinogen, Ang-I, and Ang-II from plasma could not enter into the eye,[21] suggesting that RAS components in the ocular tissues are locally synthesized, which is affirmed by Brandt et al after finding the renin mRNA in the eye.[17] These findings suggest that the presence of RAS components in ocular tissues play a pivotal role in the ocular pathophysiology.

Ocular renin-angiotensin system (RAS) signaling cascades

Angiotensin II-dependent signaling cascades

On the basis of literature, RAS signaling cascades in the eye are represented in Fig. 1. The circulatory RAS components are unable to enter into ocular cells,[21] but Milenkovic et al found that systemic infusion of Ang-II into mice decreases renin expression in the kidney and reduces the renin mRNA levels in both retinal pigment epithelium (RPE) cells and neuronal retina, whereas systemic application of ACE inhibitors (ACEIs) increased renin expression in RPE by 20-fold, suggesting that the circulatory RAS can modulate the ocular RAS.[18] In ocular tissues, Ang-II modulates the ocular physiology either from local production or systemic circulation. Ang-II is produced by classical enzyme ACE and also catalyzed by ACE-independent pathways, e.g. via chymase,[53] which is also expressed in the eye.[32] In addition, recently angiotensin converting enzyme type 2 (ACE2) is also found in the eye,[24,25,41] which can catalyze Ang-I to angiotensin (1–9) and Ang-II to angiotensin (1–7), which act oppositely to Ang-II.[41] angiotensin (1–7) mainly acts through novel angiotensin receptor type, Mas receptor, a G-protein coupled receptor encoded by Mas proto-oncogene found first in mouse kidney.[54] The Mas receptor acts opposite to AT_1R to induce vasodilatation, antiproliferation, antifibrosis, and also plays a role in fluid volume homeostasis.[55] Mas receptor is also expressed in ocular tissues particularly in the retina and ciliary body.[50,51]

In the eye, Ang-II activates AT_1R, a G-protein coupled receptor which is associated with G_q protein and triggers inositole-1,4,5-triphosphate (IP3)/Ca^{2+}[2,56,57] and diacyl glycerol/protein kinase-C (DAG/PK-C) signaling cascades,[58,59] which leads to increase intracellular Ca^{2+} through transient release of Ca^{2+} from endoplasmic reticulum via IP3 receptor and transient receptor potential-V2 (TRPV2) channels, which is present in the RPE cells.[56,57] The Ang-II/AT_1R mediated IP3/DAG signaling cascades further potentiates of inflammatory/angiogenic molecules in the diseases conditions, such as vascular endothelial growth factor (VEGF),[60–64] extracellular signal-regulated kinase (ERK),[65,66] mitogen-activated protein kinase (MAPK),[66] nuclear factor-kappaB (NF-κB), intracellular adhesion molecule-1 (ICAM-1),[67] transforming growth factor-β1 (TGF-β1),[68] nicotinamide adenine dinucleotide phosphate (NADP(H)) oxidase[69] and advanced glycation end products (AGE) accumulation[70,71] thus leading to disruption of intracellular signaling and cellular growth. These findings provide strong evidence that RAS, especially Ang-II/AT_1R signaling, is not just a regulator of cardio-renal physiology but also regulates an inflammatory and ocular physiology.

Angiotensin II independent signaling cascades

Apart from AT_1R, (P)RR also regulates blood pressure and cell function, including proliferation, angiogenesis, inflammation, and stimulation of growth factor.[72] The (P)RR binds both with renin and prorenin to exert the catalytic efficiency of renin and activate (P)RR without conventional proteolysis of prorenin prosegments,[73,74] thus induces signal transduction pathway that is independent to Ang-II. Renin and prorenin not only activate the (P)RR but also increase the formation of Ang-II, through increase in renin activity.[68] Moreover, binding of renin and prorenin also stimulate phosphorylation of (P)RR on serine and tyrosine residues, which associated with phosphorylation of ERK1/2 and an induction of MAPK.[74] Huang et al (2007) reported similar findings that prorenin binds with (P)RR, induces TGF-β, fibronectin, and collagen via ERK1/2.[75] These findings suggest that inhibition of (P)RR might play an important role in organ protection that cannot be achieved with conventional Ang-II blockade. Thus, (P)RR regulates the organ physiology, including cardiorenal[73,76] and ocular functions.[42,77]

All of these possible signaling pathways (Fig. 1) play an important role in the regulation of ocular pathophysiology. The effects of these signaling cascades of the ocular RAS may be controlled with RAS inhibitors such as ACEIs, angiotensin II Type 1 receptor blockers (AT_1RBs), and (P)RR blockers ((P)RRBs).

Ocular disorders and renin-angiotensin system (RAS)

The ocular disorders like DR, AMD, glaucoma, and cataract are leading causes of blindness worldwide.[78] All of these blinding disorders (except cataract) occur in the retina, which consists of neurons, glia, pigment epithelium and blood vessels. These ocular disorders are associated with the local or systemic neuronal and vascular homeostasis.[12] The findings of the ocular RAS in retinal cells imply various physiological functions within the eyes and associated with those blinding disorders. In the eye, Ang-II has an important role in the ocular pathophysiology; the above discussions illustrates that

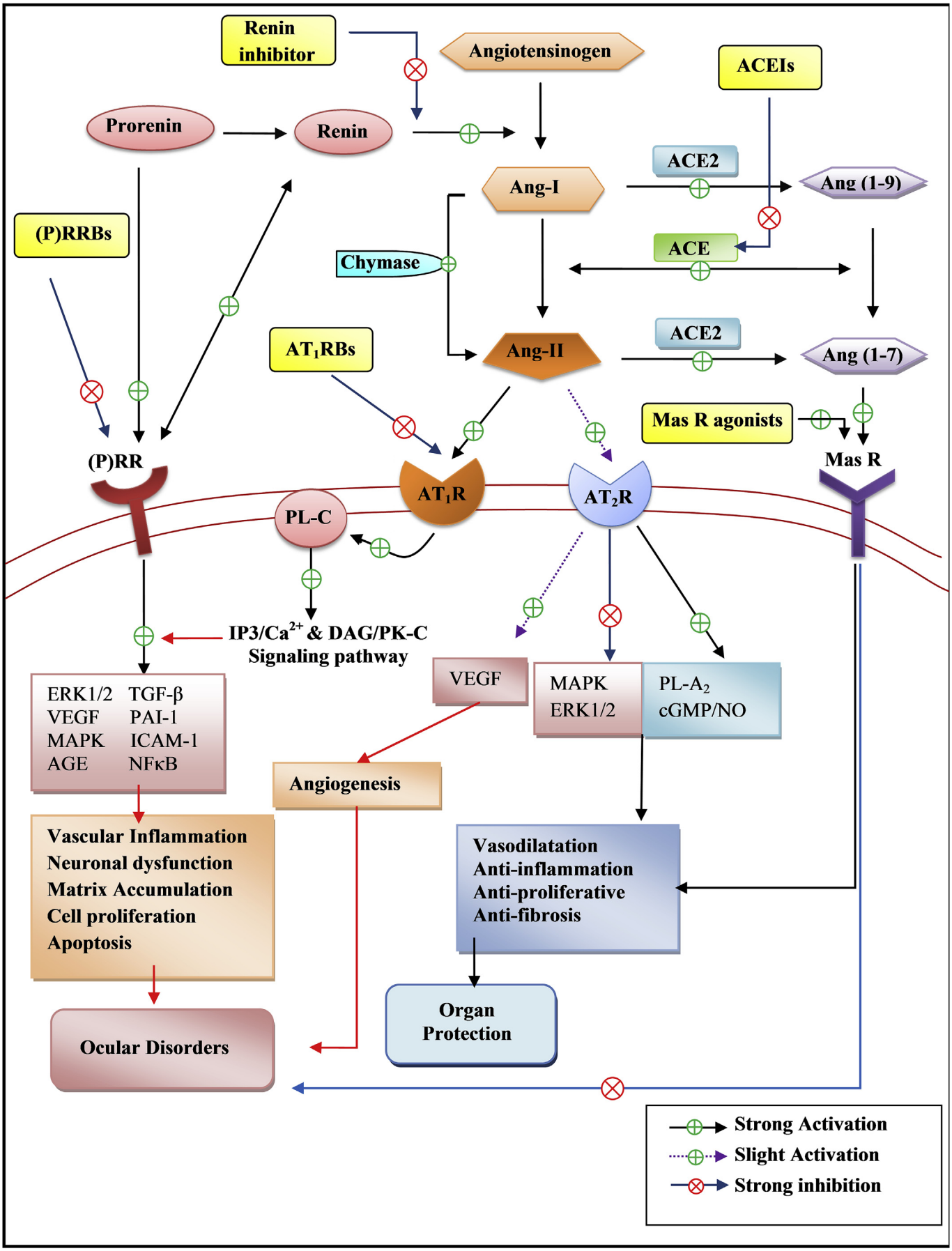
Renin inhibitor
Angiotensinogen
ACEIs
Prorenin
Renin
ACE2
Ang-I
Ang (1-9)
(P)RRBs
ACE
Chymase
AT1RBs
Ang-II
ACE2
Ang (1-7)
Mas R agonists
(P)RR
AT1R
AT2R
Mas R
PL-C
IP3/Ca2+ & DAG/PK-C Signaling pathway
VEGF
MAPK ERK1/2
PL-A2 cGMP/NO
ERK1/2 TGF-β VEGF PAI-1 MAPK ICAM-1 AGE NFκB
Angiogenesis
Vascular Inflammation
Neuronal dysfunction
Matrix Accumulation
Cell proliferation
Apoptosis
Vasodilatation
Anti-inflammation
Anti-proliferative
Anti-fibrosis
Organ Protection
Ocular Disorders
Strong Activation
Slight Activation
Strong inhibition

Table 2
Renin-angiotensin system (RAS) signaling pathways in ocular disorders.

Diseases	RAS Signaling pathway	Species	RAS modulators	References
Diabetic retinopathy	AT_1R and (P)RR signaling potentiate angiogenic and inflammatory action in the eye.	Human, rat, mice, bovine	ACEIs protect DR by reducing the over expression of VEGF in retina. AT_1RBs protect DR by reducing inflammatory response and oxidative stress in the eye. (P)RRB abolishes the angiogenic action of ERK signaling molecules. ACE2 protects retinal ganglion cell death.	61–63,67,69,70,79–87
Glaucoma	AT_1R signaling regulates aqueous humor formation, secretion, uveoscleral outflow, and IOP. Mas receptor signaling reduces the IOP.	Human, monkey, rabbit, rat, bovine	ACEIs reduce IOP by reducing aqueous humor formation and increasing uveoscleral outflow. AT_1RBs reduce IOP by increasing uveoscleral outflow. Ang (1–7) reduces IOP via Mas receptor signaling pathway. ACE2 activation reduces IOP.	49,87–97
Age-related macular degeneration	AT_1R and (P)RR signaling potentiate macular degeneration in the eye.	Human, rat, mice	ACEIs, AT_1RBs, and (P)RRBs prevent progression of choroidal neo-vascularization through suppression of inflammatory response of RAS signaling.	66,98–101
Uveitis	AT_1R and (P)RR signaling potentiate ocular inflammation.	Rat, mice	AT_1RBs and (P)RRBs downregulate the expression of inflammatory molecules. ACE2 activation protects endotoxin-induced uveitis.	42,102–107
Cataract	RAS activation potentiates oxidative stress and ionic imbalance in the eye lenses.	Rat	ACEIs prevent the progression of cataract by restoring antioxidants defense system and ionic imbalance.	108–110

ACE2: angiotensin-converting enzyme type 2; ACEIs: angiotensin-converting enzyme inhibitors; Ang (1–7): angiotensin (1–7); AT_1R: angiotensin II type 1 receptor; AT_1RBs: angiotensin II type 1 receptor blockers; IOP: intra ocular pressure; (P)RR: (pro)renin receptor; (P)RRBs: (pro)renin receptor blockers; RAS: renin-angiotensin system; VEGF: vascular endothelial growth factor.

Ang-II and its receptor, AT_1R mostly abundant in retinal cells, including Muller cells, RPE, blood vessels, and ganglion cells and are involved in the pathogenesis of those blinding ocular disorders. The RAS signaling pathways in the particular ocular diseases are represented in Table 2.

Diabetic retinopathy

DR is one of the most common microvascular complication of diabetes mellitus.[111] Many factors are involved in the pathogenesis of DR such as metabolic disorders like hyperglycemia, high blood pressure, hyperlipidemia, age, and oxidative stress.[59,112] It is reported that hyperglycemia induces the inflammatory response, oxidative stress,[12] AGE accumulation,[70,71] expression of growth factors, including VEGF,[113,114] TGF-β, pigment epithelium-derived growth factor,[58] insulin-like growth factor-1[59] in the eye and finally leads to the development of DR.

Several clinical and experimental research have shown that RAS plays an important role in the progression of DR,[12,60,115] presumably through Ang-II/AT_1R mediated actions.[116–118] Ang-II potentiates VEGF/VEGFR-2 mediated angiogenesis[63,114] and increase the permeability of retinal blood vessels, thus, it may increase the risk of neovascularization[119] and hyperpermeability.[120] Ang-II, VEGF,[121,122] and prorenin[13,123] have found to be overexpressed in the vitreous humor of proliferative diabetic retinopathy (PDR) and DR patients. ACEIs have been shown to produce the protective effect on DR through reduction of retinal VEGF/VEGFR-2 overexpression in various preclinical and clinical studies.[61,62,79,80] Whereas, Pradhan et al (2002) found that enalapril, an ACE inhibitor, at low dose did not significantly reduce the progression of moderate to severe DR in normotensive Type 2 diabetic patients,[124] suggesting that low dose of ACEIs did not block the ocular RAS sufficiently enough to exert an effect.

Fig. 1. Schematic representation of ocular renin-angiotensin system signaling cascades on the basis of literature.[2,12,41,50,51,53–77] ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme type 2; ACEIs: angiotensin-converting enzyme inhibitors; AGE: advanced glycation end products; Ang (1–7): angiotensin (1–7); Ang (1–9): angiotensin (1–9); Ang-I: angiotensin I; Ang-II: angiotensin II; AT_1R: angiotensin II type 1 receptor; AT_1RBs: angiotensin II type 1 receptor blockers; AT_2R: angiotensin II type 2 receptor; cGMP/NO: cyclic guanosine mono phosphate/nitric oxide; DAG: diacyl glycerol; ERK1/2: extracellular signal regulated kinase 1/2; ICAM-1: Intercellular adhesion molecule-1; IP3: inositole-1,4,5-triphosphate; MAPK: mitogen-activated protein kinase; Mas R: Mas receptor; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; PAI-1: plasminogen activator inhibitor-1; PK-C: protein kinase-C; PLA_2: phospholipase-A_2; PL-C: phospholipase-C; (P)RR: (pro)renin receptor; (P)RRBs: (pro)renin receptor blockers; TGF-β: transforming growth factor- β; VEGF: vascular endothelial growth factor.

Moreover, it was also found that AT_1RBs effectively block diabetes-induced inflammatory response and oxidative stress in the eye such as VEGF,[63,67,81] AGE,[81] NF-κB, ICAM-1,[67] NADP(H) oxidase[69,82] and enhance the neuroprotective markers, including brain-derived neurotrophic factor, ciliary neurotrophic factor, tyrosine hydroxylase, glutathione and caspase activity.[69] Furthermore, Miller et al found that AT_1RBs also restore the Ang-II mediated downregulation of glyoxalase-I in retinal vascular cells, which is a key regulator of AGE formation.[70]

Although these multiple events indicate that blockade of AT_1R may have beneficial effects on DR, the Diabetic Retinopathy Candesartan Trials (DIRECT) failed to show a beneficial effect of Candesartan on retinopathy progression in the type 1 diabetes patients.[125] Failure of the DIRECT programme suggested that the pathogenesis of DR also independent from Ang-II/AT_1R signaling. This hypothesis is supported by the biological action of a novel receptor (P)RR, a part of the RAS signaling, which is present in retinal Muller cells,[42] which is a site of VEGF synthesis and its tyrosine kinase receptors,[126] indicating an independent role in the pathogenesis of DR. Further studies provide the evidence that (P)RR triggers the expression of angiogenic molecules, including VEGF/VEGFR2, ERK1/2 and TGFβ1 in the retinal cells and leads to DR, which was abolished by (P)RR/ERK signaling blockade.[83−86] Recently Foureaux et al found that the activation of ACE2 reduced the death of retinal ganglion cells in hyperglycemic rats.[87] The overall findings suggest that the RAS is strongly involved in the pathogenesis of DR and inhibition of these RAS signaling events may have a beneficial effects on the reduction and prevention of DR and improves aspects of vascular and neuroglial injury in diabetic retina.

Glaucoma

Glaucoma, is the multifactorial long-term ocular neuropathy, is generally associated with a progressive loss of retinal nerve fibers and visual field.[127] It is characterized by elevated intraocular pressure (IOP) and long-term ocular neuropathy, which is associated with several risk factors, including systemic hypertension, vascular dysfunction, and diabetes.[128−131] The most important pathophysiological feature of the diseases is neurodegeneration of retinal ganglion cells that leads to increasing IOP. Most of the RAS components including ACE, Ang-II, and AT_1R are present in retinal ganglion cells and ciliary body, which regulate IOP in the eye. It is known that ciliary body secrete aqueous humor. Cullinane et al found that the RAS components in cultured human non-pigmented ciliary epithelial cells are particularly responsible for aqueous humor formation and secretion.[88] It is reported that Ang-II induces cell proliferation in bovine trabecular meshwork cells,[89] which is involved in aqueous humor outflow and diminishes uveoscleral out-flow.[90] These findings indicate that the ocular RAS may implicate in the formation of aqueous humor, its drainage and regulation of IOP. Therefore, several researchers showed that inhibition of RAS through ACE inhibition[91,92] and AT_1R blockade[93,94] have beneficial effects in both normotensive and glaucomatous eyes. ACEIs trigger the synthesis of prostaglandins by preventing the breakdown of bradykinin, which leads to lowering of IOP by increasing uveoscleral outflow.[95] Additionally, it also reduces aqueous humor formation by reducing blood flow in the ciliary body.[96] AT_1RBs may be slightly increased uveoscleral outflow[94] and effectively suppresses retinal ganglion cell death.[132,133]

Moreover, the Mas receptor[50] and ACE2[25] are also expressed in the ocular tissues, which may also regulate the ocular physiology. Thereby, Mas receptor activator, angiotensin (1−7),[49] and ACE2 activator, diminazene aceturate (DIZE)[87,97] showed beneficial effects for glaucoma management via a decrease in IOP. These findings indicate that RAS inhibition may be effective for treatment of glaucoma.

Age-related macular degeneration

The World Health Organization reported that AMD is responsible for 8.7% of blindness worldwide.[77] Generally, it is characterized by choroidal neovascularization (CNV; wet AMD), and atrophy of RPE and photoreceptor cells (dry AMD).[12] Wet AMD is developed through ocular inflammation, infiltration of macrophages, and AGE formation, and the main mediator is VEGF.[134−136] At present, wet AMD is treated with the VEGF inhibitors.[137,138] The presence of RAS components in the ocular tissues including RPE, choroid, and photoreceptor cells and its inflammatory response, suggesting that deregulation of RAS may enhance the risk of AMD.[98,139,140] The activation of AT_1R and (P)RR in the eye, potentiate the ERK1/2, VEGF, ICAM-1, and monocyte chemoattractant protein-1expression in the ocular tissues and leads to DR and AMD.[99,100] Therefore, AT_1RBs,[66,101] ACEIs,[98] and (P)RRBs[100] prevent progression of CNV through suppression of such inflammatory molecules. These findings suggested that the controlling of RAS may provide a pivotal strategy to reduce the progression of wet AMD. At present, effective therapies are not available for dry AMD, but nutritional supplements may slow the progression of the disease.[141] Alcazar et al showed (P)RR is involved in the pathology of dry AMD, suggesting that in the future, RAS may play an important role to manage dry AMD.[44]

Uveitis

Hyperactivation of RAS involved in the overexpression of the inflammatory response and immune function. It stimulates accumulation of neutrophils,[142] differentiation of dendritic cells[143] and production of inflammatory chemokines by vascular endothelial cells.[144] Endotoxin-induced uveitis[42,102] and experimental autoimmune uveoretinitis[103] models upregulate expression of proinflammatory and adhesion molecules like ICAM-1, interferon-γ and interleukin-6. These molecules inhibited by AT_1RBs[102−106] and (P)RRBs.[42] Recently, Qiu et al reported that activation of endogenous ACE2 by DIZE showed the preventive effects on endotoxin-induced uveitis mouse model.[107] All these findings support that the regulation of RAS may play a beneficial role in the treatment of uveitis.

Cataract

Cataractous opacification of the lens is one of leading causes of visual dysfunction and contributes to 50% of blindness worldwide.[145] Progression of cataract depends on several risk factors such as diabetes and systemic hypertension.[146] At present, there is no evidence to find the presence of RAS components in eye lenses, but hyperactivation of RAS through diabetes and systemic hypertension[65,147,148] can modulate the production of AGE,[70,71] reactive oxygen species,[58] and electrolyte homeostasis,[94] which might be responsible for the increase in the incidence of cataract formation. Moreover, we previously reported that RAS activation via two-kidney, one clip model significantly modulates the oxidative stress and ionic imbalance in eye lenses and further leads to the development of cataract in the hypertensive state, which is prevented by administration of angiotensin converting enzyme inhibitor (ramipril).[108] Additionally, several researchers found that ACE inhibition showed beneficial effects in reduction of the cataract through the restoration of the ionic balance (Na^+/K^+), free radical scavenging activity, enhanced the enzymatic and non-enzymatic defense mechanism as well as inhibition of AGE production.[109,110] Therefore, it may be hypothesized that the ocular RAS has an important role to play in regulation of lenticular physiology and blockade of Ang-II mediated action through ACEIs and AT_1RBs may reduce the progression of cataract particularly in diabetes and hypertensive conditions.

In conclusion, the classical RAS are known as blood pressure as well as electrolyte homeostasis regulator. Recently, it has been recognized as a proinflammatory mediator and involved in the various age-related ocular disorders through exacerbation of the inflammatory molecules. The findings of the RAS components in the eye initiate a new therapeutic approach to attenuate the ocular disorders through RAS inhibitors such as ACEIs and AT_1RBs. The new RAS modulators like renin inhibitors, (P)RRBs, AT_2R, Mas receptor have shown potential role in the circulatory as well as local RAS modulation and had beneficial effects on the management of cardio-renal and ocular disorders. The present review describes the ocular RAS in the pathophysiology of such ocular disorders and effects of classical and newer RAS inhibitors in respect of pathogenic inflammatory molecules that elicit the newer approach in ophthalmic research. In future novel RAS components like Ang-III, Ang-IV, and its receptor AT_4R may also have an important ocular physiology. Therefore, the work to develop the novel and selective RAS inhibitors may hold great promise to attenuate ocular disorders and help to treat life-threatening blinding disorders.

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