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

Reviewed 27 June 2016; revised 27 September 2016; accepted 30 September 2016
Available online 20 October 2016

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 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.

Copyright © 2017, Iranian Society of Ophthalmology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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. The circulatory RAS system initiates with renin which cleaves angiotensinogen to form the decapeptide angiotensin I (Ang-I) which is then converted to octapeptide angiotensin II (Ang-II) by the angiotensin-converting enzyme (ACE). Ang-II regulates various biological effects through the activation of Angiotensin II type I receptors (AT₁R) and Angiotensin II type 2 receptors (AT₂R). Ang-II elicits most of its well-known biological effects, including vasoconstriction, electrolyte homeostasis, fibrosis, inflammation, and proliferation through activation of AT₁R. The actions of the AT₂R are not so much defined, but they possibly oppose the actions of the AT₁R like vasodilatory effects. However, findings indicate that AT₂R acts similar to AT₁R, like promoting cell growth, apoptosis, and angiogenesis in some tissues.

Plenethora researchers highlighted the significance of the local RAS in various extrarenal tissues, including the adrenal glands, thymus, and ocular tissues. The presence and
functional role of the RAS components, including prorenin, renin, ACE, angiotensinogen, Ang-II, (pro)renin receptor ((P)RR), and AT1R 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

| 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 | Porcine | 13,21 |
| 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 | |
|                | 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 | 2.19,20,23,25–29 |
|                | Ciliary body | Human, rabbit, rat, porcine | |
|                | Aqueous fluid | Human, monkey, dog, rabbit | |
|                | Vitreous fluid | Monkey, dog, rabbit | |
|                | Tear fluid | Human, rabbit | |
|                | Cornea, conjunctiva | Human, rabbit, porcine | |
|                | Iris | Human, monkey, dog | |
|                | Sclera | Human, rodent, porcine | 24.25,40,41 |
| ACE2           | Retina | Human | |
| Chymase        | Vitreous fluid | Human | 32 |
| (P)RR          | Retina (Muller cells, RPE, ganglion cells), choroid, iris, ciliary body, cornea, conjunctiva | Human | 2.42–44 |
| AT1R           | Retina (Muller cells, amacrine cells, RPE, blood vessels, photoreceptors, ganglion cells), choroid, cornea, ciliary body, iris, conjunctiva | Human | 2.18,23,24,45–48 |
| AT2R           | 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; AT1R: angiotensin II type 1 receptor; AT2R: 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. 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 lack to identify the origin of the ocular RAS, either local production or selective uptake by ocular tissues from the circulatory RAS. 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, 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. 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, 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. 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, which is also expressed in the eye. In addition, recently angiotensin converting enzyme type 2 (ACE2) is also found in the eye, which can catalyze Ang-I to angiotensin (1–9) and Ang-II to angiotensin (1–7), which act oppositely to Ang-II, mainly acts through novel angiotensin receptor type, Mas receptor, a G-protein coupled receptor encoded by Mas proto-oncogene found first in mouse kidney. The Mas receptor acts opposite to AT1R to induce vasodilatation, antiproliferation, antifibrosis, and also plays a role in fluid volume homeostasis. Mas receptor is also expressed in ocular tissues particularly in the retina and ciliary body.

In the eye, Ang-II activates AT1R, a G-protein coupled receptor which is associated with Gq protein and triggers inositol-1,4,5-triphosphate (IP3)/Ca2+ and diacyl glycerol/protein kinase-C (DAG/PK-C) signaling cascades, which leads to increase intracellular Ca2+ through transient release of Ca2+ from endoplasmic reticulum via IP3 receptor and transient receptor potential-V2 (TRPV2) channels, which is present in the RPE cells. The Ang-II/AT1R mediated IP3/DAG signaling cascades further potentiates of inflammatory/angiogenic molecules in the diseases conditions, such as vascular endothelial growth factor (VEGF), extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), nuclear factor-kappaB (NF-kB), intracellular adhesion molecule-1 (ICAM-1), transforming growth factor-β1 (TGF-β1), nicotinamide adenine dinucleotide phosphate (NADP(H)) oxidase and advanced glycation end products (AGE) accumulation thus leading to disruption of intracellular signaling and cellular growth. These findings provide strong evidence that RAS, especially Ang-II/AT1R 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 AT1R, (P)RR also regulates blood pressure and cell function, including proliferation, angiogenesis, inflammation, and stimulation of growth factor. 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, 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. 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. The (P)RR binds with (P)RR, induces TGF-β, fibroactin, and collagen via ERK1/2. 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 and ocular functions.

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 (AT1RBs), 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. 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. 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
Diabetic retinopathy

Ang-II and its receptor, AT₁R 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.

**Table 2**

| Diseases                        | RAS Signaling pathway | Species                       | RAS modulators                                      | References |
|--------------------------------|-----------------------|-------------------------------|-----------------------------------------------------|------------|
| Diabetic retinopathy           | AT₁R and (P)RR signaling potentiates angiogenic and inflammatory action in the eye. | Human, rat, mice, bovine   | ACEIs protect DR by reducing the over expression of VEGF in retina. AT₁RBs protect DR by reducing inflammatory response and oxidative stress in the eye. (P)RRBs abolishes the angiogenic action of ERK signaling molecules, ACE2 protects retina and ganglion cell death. | 61–63,87,89,90,97 |
| Glaucoma                       | AT₁R 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. AT₁RBs reduce IOP by increasing uveoscleral outflow. Ang (1–7) reduces IOP via Mas receptor signaling pathway. ACE2 activation reduces IOP. | 49,87–97,66,98–101 |
| Age-related macular degeneration| AT₁R and (P)RR signaling potentiates macular degeneration in the eye. | Human, rat, mice | ACEIs, AT₁RBs, and (P)RRBs prevent progression of choroidal neo-vascularization through suppression of inflammatory response of RAS signaling. | 42,102–107 |
| Uveitis                        | AT₁R and (P)RR signaling potentiates ocular inflammation. | Rat, mice | AT₁RBs and (P)RRBs downregulate the expression of inflammatory molecules. ACE2 activation protects endotoxin-induced uveitis. | 108–110 |
| 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. | 40,121–123 |

ACE2: angiotensin-converting enzyme type 2; ACEIs: angiotensin-converting enzyme inhibitors; Ang (1–7): angiotensin (1–7); AT₁R: angiotensin II type 1 receptor; AT₁RBs: 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.

DR is one of the most common microvascular complication of diabetes mellitus. It is reported that hyperglycemia induces the inflammatory response, oxidative stress. AGE accumulation, expression of growth factors, including TGF-β, pigment epithelium-derived growth factor, insulin-like growth factor-1 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, presumably through Ang-II/AT₁R mediated actions and Ang-II potentiates VEGF/VEGFR-2 mediated angiogenesis and increase the permeability of retinal blood vessels, thus, it may increase the risk of neovascularization and hyperpermeability. Ang-II, VEGF, and prorenin 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, 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, suggesting that low dose of ACEIs did not block the ocular RAS sufficiently enough to exert an effect.
Moreover, it was also found that AT1R/βs effectively block diabetes-induced inflammatory response and oxidative stress in the eye such as VEGF, AGE, NF-kB, ICAM-1, NADP(H) oxidase, and enhance the neuroprotective markers, including brain-derived neurotrophic factor, ciliary neurotrophic factor, tyrosine hydroxylase, glutathione and caspase activity. Furthermore, Miller et al found that AT1R/βs also restore the Ang-II mediated downregulation of glyoxalase-I in retinal vascular cells, which is a key regulator of AGE formation.

Although these multiple events indicate that blockade of AT1R 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. 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, which is a site of VEGF synthesis and its tyrosine kinase receptors, 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/VGFR2, ERK1/2 and TGFβ1 in the retinal cells and leads to DR, which was abolished by (P)RR/ERK signaling blockade. Recently Foureaux et al found that the activation of ACE2 reduced the death of retinal ganglion cells in hyperglycemic rats. 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. 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. 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 AT1R 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. It is reported that Ang-II induces cell proliferation in bovine trabecular meshwork cells, which is involved in aqueous humor outflow and diminishes uveoscleral outflow. 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 and AT1R blockade 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. Additionally, it also reduces aqueous humor formation by reducing blood flow in the ciliary body. AT1R/βs may be slightly increased uveoscleral outflow and effectively suppresses retinal ganglion cell death.

Moreover, the Mas receptor and ACE2 are also expressed in the ocular tissues, which may also regulate the ocular physiology. Thereby, Mas receptor activator, angiotensin (1–7), and ACE2 activator, dimazene aceturate (DIZE) 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. Generally, it is characterized by choroidal neovascularization (CNV; wet AMD), and atrophy of RPE and photoreceptor cells (dry AMD). Wet AMD is developed through ocular inflammation, infiltration of macrophages, and AGE formation, and the main mediator is VEGF. The activation of ACE2 reduced the death of retinal ganglion cells in hyperglycemic rats. 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. Age-related macular degeneration (AMD), and atrophy of RPE and photoreceptor cells (dry AMD). Wet AMD is developed through ocular inflammation, infiltration of macrophages, and AGE formation, and the main mediator is VEGF. The activation of ACE2 reduced the death of retinal ganglion cells in hyperglycemic rats. 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. AMD), and atrophy of RPE and photoreceptor cells (dry AMD). Wet AMD is developed through ocular inflammation, infiltration of macrophages, and AGE formation, and the main mediator is VEGF. The activation of ACE2 reduced the death of retinal ganglion cells in hyperglycemic rats. 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.
Cataract
Cataractous opacification of the lens is one of leading causes of visual dysfunction and contributes to 50% of blindness worldwide. Progression of cataract depends on several risk factors such as diabetes and systemic hypertension. 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 can modulate the production of AGE, reactive oxygen species, and electrolyte homeostasis, 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). 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. 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 AT1R 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 AT1R. The new RAS modulators like renin inhibitors, (P)RRBs, AT2-R, 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 AT2R 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.

References
1. Fyhquist F, Saijonmaa O. Renin-angiotensin system revisited. J Intern Med. 2008;264:224–236.
2. White AJR, Cheruvu SC, Sarris M, et al. Expression of classical components of the renin-angiotensin system in the human eye. J Renin Angiotensin Aldosterone Syst. 2015;16:59–66.
3. Cheng ZJ, Vapaatalo H, Mervaala E. Angiotensin II and vascular inflammation. Med Sci Monit. 2005;11:RA194–205.
4. Culman J, Hohle S, Qadri F, et al. Angiotensin as neuromodulator/neurotransmitter in central control of body fluid and electrolyte homeostasis. Clin Exp Hypertens. 1995;17:281–293.
5. Qi GM, Jia LX, Li XL, Du J. Adiponectin suppresses angiotensin II-induced inflammation and cardiac fibrosis through activation of macrophage autophagy. Endocrinology. 2014;155:2254–2265.
6. Chung O, Kuhl H, Stoll M, Unger T. Physiological and pharmacological implications of AT1 versus AT2 receptors. Kidney Int. 1998;67:595–599.
7. Cao Z, Kelly DJ, Cox A, et al. Angiotensin type 2 receptor is expressed in the adult rat kidney and promotes proliferation and apoptosis. Kidney Int. 2000;58:2437–2451.
8. Levy BI, Benessiano J, Henrion D, et al. Chronic blockade of AT2 subtype receptor prevents the effect of angiotensin II on the rat vascular structure. J Clin Invest. 1996;98:418–425.
9. Sarlos S, Rizkalla B, Moravske CJ, Cao Z, Cooper ME. Wilkinson-Berkla JL. Retinal angiogenesis is mediated by an interaction between the angiotensin type 2 receptor, VEGF, and angiopoietin. Am J Pathol. 2003;163:879–887.
10. Gong P, Wilkinson-Berkla JL, Skinner SL. Control of renin secretion from adrenal gland in transgenic Ren-2 and normal rats. Mol Cell Endocrinol. 2001;173:203–212.
11. Wilkinson-Berkla JL, Kelly DJ, Gong P, Campbell DJ, Skinner SL. Characterization of a thymic renin-angiotensin system in the transgenic m(Ren-2)27 rat. Mol Cell Endocrinol. 2002;194:201–209.
12. Kurihara T, Ozawa Y, Ishida S, Okano H, Tsubata K. Renin angiotensin system hyperactivation can induce inflammation and retinal neural dysfunction. Int J Inflam. 2012;581695:14.
13. Daniels AH, Van den Dorpel MA, Deinum J, et al. Renin, prorenin, and immunoreactive renin in vitreous fluid from eyes with and without diabetic retinopathy. J Clin Endocrinol Metab. 1989;68:160–167.
14. Sramek SJ, Wallow IH, Day RP. Ehrlich EN. Ocular renin-angiotensin: immunohistochemical evidence for the presence of prorenin in eye tissue. Invest Ophthalmol Vis Sci. 1988;29:1749–1752.
15. Wallow IHL, Sramek SJ, Bindley CD, Darjatmoko SR, Gange SJ. Ocular renin angiotensin: immunocytochemical localization of prorenin. Curr Eye Res. 1993;12:945–950.
16. Berkla JL, Stubbs AJ, Wang DJ, et al. Renin-containing Muller cells of the retina display endocrine features. Invest Ophthalmol Vis Sci. 1995;36:1450–1458.
17. Brandt CR, Pamery AM, Micales B, et al. Renin mRNA is synthesized locally in rat ocular tissues. Curr Eye Res. 1994;13:755–763.
18. Milenkovic VM, Brockmann M, Meyer C, et al. Regulation of the renin expression in the retinal pigment epithelium by systemic stimuli. Am J Physiol Ren Physiol. 2010;299:F396–F403.
19. Ramirez M, Davidson EA, Luttenauer L, et al. J Ocul Pharmacol Ther. 1996;12:299–312.
20. Wagner J, Jan Danser AH, Derkx FH, et al. 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 Pharmacol. 1996;80:159–163.
21. Danser AH, Derkx FH, Admiraal PJ, Deinum J, De Jong PT, Schalekamp MA. Angiotensin levels in the eye. Invest Ophthalmol Vis Sci. 1994;35:1008–1018.
22. Goei AK, Jabbour NM. Vitreous level of angiotensin-II in patients with diabetic retinopathy, Invest Ophthalmol Vis Sci. 1991;32:1027.
23. Savaskan E, Lofller K, Meier F, Muller FS, Flammer J, Meyer P. Immunohistochemical localization of angiotensin-converting enzyme, angiotensin II and angiotensin AT1 receptor in human ocular tissues. Ophthalmic Res. 2004;36:312–320.
24. Senanayake P, Drazba J, Shadrach K, et al. Angiotensin II and its receptor subtypes in the human retina. Invest Ophthalmol Vis Sci. 2007;48:3301–3311.
25. Hoilappa M, Valjakka J, Väänänen A. Angiotensin (1–7) and ACE2, “the hot spots” of renin-angiotensin system, detected in the human aqueous humor. Open Ophthalmol J. 2015;9:25–32.
26. Ferrari DG, Ryan JW, Rockwood EJ, Davis EB, Anderson DR. Angiotensin-converting enzyme in bovine, feline, and human ocular tissues. Invest Ophthalmol Vis Sci. 1988;29:876–881.
27. Geng L, Persson K, Nilsson SFE. Angiotensin converting enzyme (ACE) activity in porcine ocular tissue: effects of diet and ACE inhibitors. J Pharm Ther. 2003;19:589–596.

28. Ilic R, Kojovic V. Angiotensin I converting enzyme (kininase II) in ocular tissues. Exp Eye Res. 1980;30:299–303.

29. Ikemoto F, Yamamoto K. Renin angiotensin system in the aqueous humor of rabbits, dogs and monkeys. Exp Eye Res. 1978;27:723–725.

30. Immonen I, Friberg K, Sorsila R, Fayhrquist F. Concentration of angiotensin-converting enzyme in tears of patients with sarcoidosis. Acta Ophthalmol Copenhagen. 1987;65:27–29.

31. Kida T, Ikeda T, Nishimura M, et al. Renin-angiotensin system in porcine ocular tissue: a noninvasive test for evaluation of ocular sarcoidosis. Eur J Ophthalmol. 2006;16:177–183.

32. Maruichi M, Oku H, Takai S, et al. Measurement of activities in two different angiotensin II generating systems, chymase and angiotensin-converting enzyme, in the vitreous fluid of vitreoretinal diseases: a possible involvement of chymase in the pathogenesis of macular hole patients. Curr Eye Res. 2004;29:321–325.

33. Sharma OP, Vita JB. Determination of angiotensin converting enzyme in tears: a noninvasive test for evaluation of ocular sarcoidosis. Arch Ophthalmol. 1983;101:559–561.

34. Shiota N, Saegusa Y, Nishimura K, Miyazaki M. Angiotensin II generation of retinal vessels. Invest Ophthalmol. 2003;47:36–41.

35. Strittmatter SM, Braas KM, Snyder SH. Localisation of angiotensin-converting enzymes ACE1 and ACE2 and inhibition by bioactive peptides in porcine ocular tissue. Invest Ophthalmol Vis Sci. 2005;46:2686–2692.

36. Wilkinson-Berka JL, Miller AG, Fletcher EL. Prorenin and the (pro)renin receptor: do they have a pathogenic role in the retina? Front Biosci Elite Ed. 2010;2:1054–1064.

37. Busolini E, Foa AM, Lavía CA, et al. Recent developments in the management of dry age-related macular degeneration. Clin Ophthalmol. 2015;9:563–574.

38. Downie LE, Vessey K, Miller A, et al. Neuronal and glial cell expression of angiotensin II type 1 (AT1) and type 2 (AT2) receptors in the rat retina. Neuroscience. 2009;161:195–213.

39. Fletcher EL, Phipps JA, Ward MM, Vessey KA, Wilkinson-Berka JL. The renin-angiotensin system in retinal health and disease: its influence on neurons, glia and the vasculature. Prog Retin Eye Res. 2010;29:284–311.

40. Murata M, Nakagawa M, Takashiki S. Expression and localization of angiotensin II type I receptor mRNA in rat ocular tissues. Ophthalmologica. 1997;211:384–386.

41. Wheeler-Schilling TH, Kohler K, Sautter M, Guenther E. Angiotensin II receptor subtype gene expression and cellular localization in the retina and non-neuronal ocular tissues of the rabbit. Euro J Neurosci. 1999;11:3387–3394.

42. Vaajanan A, Vapaatalo H, Kautiainen H, Oksala O. Angiotensin (1–7) reduces intraocular pressure in the normotensive rabbit eye. Invest Ophthalmol Vis Sci. 2008;49:2557–2562.

43. Vaajanan A, Lakkisto P, Virtanen I, et al. Angiotensin receptors in the eyes of arterial hypertensive rats. Acta Ophthalmol. 2010;88:431–438.

44. Vaajanan A, Kalesnykas G, Vapaatalo H, Uusitalo H. The expression of Mas-receptor of the renin-angiotensin system in the human eye. Graefes Arch Clin Exp Ophthalmol. 2015;253:1053–1059.

45. Ilic R, Robinson CJG, Erods EG. Angiotensin I converting enzyme activity in the choroid plexus and in the retina. In: Buckley JP, Ferrario CM, eds. Central actions of Angiotensin and Related Hormones. New York: Pergamon Press, 1977:23–27.

46. Kriz W, Mogielnicki A, Buczko W. The physiological significance of the alternative pathways of angiotensin II production. J Physiol Pharmacol. 2006;57:529–539.

47. Santos RA, Simoes e Silva AC, Marie C, et al. Angiotensin (1–7) is an endogenous ligand for the G-protein-coupled receptor Mas. Proc Natl Acad Sci USA. 2003;8:8258–8263.

48. Kosten E, Milligan G, Christopoulos A, et al. G-protein-coupled receptor Mas is a physiological antagonist of the angiotensin II type I receptor. Circulation. 2005;111:1806–1813.

49. Barro-Soria R, Stindi J, Muller C, Foeckler R, Todorov V, Castrop H. Angiotensin-2-mediated Ca2+ signaling in the retinal pigment epithelium: role of angiotensin-receptor-associated-protein and TRPV2 channel. PLoS One. 2012;7:e49624.

50. Fellner SK, Arendshorst WJ. Angiotensin II Ca2+-signaling in rat afferent arterioles: stimulation of cyclic ADP ribose and IP3 pathways. Am J Physiol Ren Physiol. 2005;288:F785–F791.

51. Boehm IH, Bosna T, Andersen HL, Porta M. The eyes in diabetes and diabetes through the eyes. Diabetes Res Clin Pract. 2007;78:S51–S58.

52. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of diabetic retinopathy. Jpn Heart J. 2013;34:35–60.

53. Funastu H, Yamashita H. Pathogenesis of diabetic retinopathy and the renin angiotensin system. Ophthalmic Physiol Opt. 2003;23:495–501.

54. Gilbert RE, Kelly DJ, Cox AJ, et al. Angiotensin converting enzyme inhibition reduces retinal overexpression of vascular endothelial growth factor and hyperpermeability in experimental diabetes. Diabetologia. 2000;43:1360–1367.

55. Moravski CJ, Kelly DJ, Cooper ME, et al. Retinal neovascularization is prevented by blockade of the renin-angiotensin system. Hypertension. 2000;36:1099–1104.

56. Nagisa Y, Shintani A, Nakagawa S. The angiotensin II receptor antagonist candesartan cilexetil (TCV-116) ameliorates retinal disorders in rats. Diabetologia. 2001;44:883–888.

57. Jolie AK, Chaturvedi N. The retinal renin-angiotensin system: implications for therapy in diabetic retinopathy. J Hum Hypertens. 2002;16:842–846.

58. Kurihara T, Ozawa Y, Nagai N, et al. Angiotensin II type 1 receptor signaling contributes to synaptophysin degradation and neuronal dysfunction in the diabetic retina. Diabetes. 2008;57:2191–2198.

59. Pons M, Cousins SW, Alcazar O, Striker GE, Marin-Castano ME. Angiotensin II-induced MMP-2 activity and MMP-14 and basigin protein expression are mediated via angiotensin II type 1 receptor-mediated protein kinase 1 pathway in retinal pigment epithelium. Am J Pathol. 2011;178:2665–2681.

60. Nagai N, Izumi-Nagai K, Oike Y, et al. Suppression of diabetes induced retinal inflammation by blocking the angiotensin II type 1 receptor or its downstream nuclear factor-kappaB pathway. Invest Ophthalmol Vis Sci. 2007a;48:4342–4350.

61. Wilkinson-Berka JL, Campbell DJ. (Pro)renin receptor: a treatment target for diabetic retinopathy? Diabetes. 2009;58:1485–1487.

62. Ola MS, Ahmed M, Abouhashish HM, Al-Rejaie SS, Alhomida AS. Telmisartan ameliorates neurotrophic support and oxidative stress in the retina of streptozocin-induced diabetic rats. Neurochem Res. 2013;38:1572–1579.

63. Miller AG, Tan G, Binger BJ, et al. Candesartan attenuates diabetic retinal vascular pathology by restoring glyoxalase-I function. Diabetes. 2010;59:3208–3215.
71. Wilkinson-Berka JL. Angiotensin and diabetic retinopathy. Int J Biochem Cell Biol. 2006;38:752–765.
72. Wilkinson-Berka JL. Prorenin and the (pro)renin receptor in ocular pathology. Am J Pathol. 2008;173:1591–1594.
73. Ichihara A, Hayashi M, Kaneshiro Y, et al. Inhibition of diabetic nephropathy by a decoy peptide corresponding to the “handle” region for nonproteolytic activation of prorenin. J Clin Invest. 2004;114: 1128–1135.
74. Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiogenesis II production and cellular responses to renin. J Clin Invest. 2002;109:1417–1427.
75. Huang Y, Noble NA, Zhang J, Xu C, Border WA. Renin-stimulated TGF-beta expression is regulated by a mitogen-activated protein kinase in mesangial cells. Kidney Int. 2007;72:45–52.
76. Kaneshiro Y, Ichihara A, Sakoda M, et al. Slowly progressive, angiogenic activity in proliferative diabetic retinopathy: a new implication. Invest Ophthalmol Vis Sci. 2007;48:422–429.
77. Satofuka S, Ichihara A, Nagai N, et al. Role of nonproteolytically activated renin in pathologic, but not physiologic, retinal neovascularization. Invest Ophthalmol Vis Sci. 2007;48:2321–2326.
78. Ishida S. Lifestyle-related diseases and anti-aging ophthalmology: suppression of retinal and choroidal pathologies by inhibiting renin-angiotensin system and inflammation. Nihon Ganka Gakkai Zasshi. 2009;113:403–422.
79. Soufoka S, Ichihara A, Nagai N, et al. (Pro)renin receptor promotes choroidal neovascularization by activating its signal transduction and tissue renin angiogenin system. Am J Pathol. 2008;173:1911–1918.
80. Nagai N, Okie Y, Izumi-Nagai K, et al. Angiotensin II type 1 receptor-mediated inflammation is required for choroidal neovascularization. Arterioscler Thromb Vasc Biol. 2006;26:2252–2259.
81. Hogeboom BIM, Polak BC, Reichert-Thoen JW, et al. Angiotensin II receptor involvement by ACE inhibitors of cataract induced by glucose. J Curr Ophthalmol. 2011;32:139–143.
82. Wilkinson-Berka JL. Prorenin and the (pro)renin receptor in ocular pathol-ogy. Am J Pathol. 2008;173:1591–1594.
83. Ichihara A, Hayashi M, Kaneshiro Y, et al. Inhibition of diabetic nephropathy by a decoy peptide corresponding to the “handle” region for nonproteolytic activation of prorenin. J Clin Invest. 2004;114: 1128–1135.
84. Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiogenesis II production and cellular responses to renin. J Clin Invest. 2002;109:1417–1427.
85. Huang Y, Noble NA, Zhang J, Xu C, Border WA. Renin-stimulated TGF-beta expression is regulated by a mitogen-activated protein kinase in mesangial cells. Kidney Int. 2007;72:45–52.
86. Kaneshiro Y, Ichihara A, Sakoda M, et al. Slowly progressive, angiogenic activity in proliferative diabetic retinopathy: a new implication. Invest Ophthalmol Vis Sci. 2007;48:422–429.
87. Vision 2020: The Right to Sight. Global Initiative for the Elimination of Avoidable Blindness: Action Plan 2006–2011. World Health Organiza-tion. http://www.who.int/blindness/Vision2020_report.pdf.
88. Hoogeboom BIM, Polak BC, Reichert-Thoen JW, et al. Angiotensin converting enzyme inhibiting therapy is associated with lower vitreous vascular endothelial growth factor concentrations in patients with proliferative diabetic retinopathy. Diabetologia. 2002;45:203–209.
89. Zheng Z, Chen H, Ke G, et al. Protective effect of perindopril on diabetic retinopathy is associated with decreased vascular endothelial growth factor-to-pigment epithelium-derived factor ratio: involvement of a mitochondria-reactive oxygen species pathway. Diabetes. 2009;58: 954–964.
90. Sugiyama T, Okuno T, Fukuhara M, et al. Angiotensin II receptor blocker inhibits abnormal accumulation of advanced glycation end products and retinal damage in a rat model of type 2 diabetes. Exp Eye Res. 2007;85:406–412.
91. White AJR, Heller JP, Leung J, Tassoni A, Martin KR. Retinal ganglion cell neuroprotection by an angiotensin II blocker in an ex vivo retinal explant model. J Renin Angiotensin Aldosterone Syst. 2015;16:1193–1201.
92. Haque R, Hur EH, Farrell AN, Iuvone PM, Howell JC. MicroRNA-152 represses VEGF and TGFβ1 expressions through post-transcriptional inhibition of (Pro)renin receptor in human retinal endothelial cells. Mol Vis. 2015;21:224–235.
93. Kanda A, Ishida S. The vitreous renin–angiotensin system is mediated by the soluble (pro)renin receptor in diabetic retinopathy: a new implication of the receptor-associated prorenin system. Taiwan J Ophthalmol. 2013; 5:31–53.
94. Kanda A, Noda K, Saito W, Ishida S. (Pro)renin receptor is associated with angiogenic activity in proliferative diabetic retinopathy. Diabetologia. 2012;55:3104–3113.
95. Satofuka S, Ichihara A, Nagai N, et al. (Pro)renin receptor-mediated signal transduction and tissue renin-angiotensin system contribute to diabetes-induced retinal inflammation. Diabetes. 2009;58:1625–1634.
96. Foureaux G, Nogueira BS, Coutinho DCO, Raizada MK, Nogueira JC, Ferreira AJ. Activation of endogenous angiotensin converting enzyme 2 prevents early injuries induced by hyperglycemia in rat retina. Braz J Med Biol Res. 2015;48:1109–1114.
97. Cullinan AB, Leung PS, Ortego J, Coca-Prados M, Harvey BJ. Renin-angiotensin system expression and secretory function in cultured human ciliary body non-pigmented epithelium. Br J Ophthalmol. 2002;86:676–683.
98. Shen F, Zhang L, Liu T. Effects of angiotensin II on the 3H-TdR incorporation and synthesis of collagen in cultured bovine trabecular meshwork cells (article in Chinese). Yan Ke Xue Bao. 2001;17:209–212.
99. Inoue T, Yokoyama T, Koike H. The effect of angiotensin II on uveoscleral outflow in rabbits. Curr Eye Res. 2001;23:139–143.
100. Mehta A, Iyer L, Parmar S, Shah G, Goyal R. Oculohypotensive effect of perindopril in acute and chronic models of glaucoma in rabbits. Can J Physiol Pharmacol. 2010;88:595–600.
101. Nagai N, Oike Y, Izumi-Nagai K, et al. Angiotensin II type 1 receptor-mediated inflammation is required for choroidal neovascularization. Arterioscler Thromb Vasc Biol. 2006;26:2252–2259.
102. Hogeboom BIM, Polak BC, Reichert-Thoen JW, et al. Angiotensin converting enzyme inhibiting therapy is associated with lower vitreous vascular endothelial growth factor concentrations in patients with proliferative diabetic retinopathy. Diabetologia. 2002;45:203–209.
103. Kanda A, Noma K, Saito W, Ishida S. (Pro)renin receptor is associated with nonproteolytic activation of prorenin. J Clin Invest. 2004;114: 1128–1135.
Otani A, Takagi H, Suzuma K, Honda Y. Angiotensin II potentiates vascular endothelial growth factor-induced angiogenic activity in retinal microcapillary endothelial cells. Circ Res. 1998;82:619–628.

Otani A, Takagi H, Oh H, et al. Angiotensin II-stimulated potentiates vascular endothelial growth factor expression in bovine retinal pericytes. Invest Ophthalmol Vis Sci. 2000;41:1192–1199.

Chaturvedi N. Modulation of renin-angiotensin system and retinopathy. Heart. 2000;84:29–131.

Clermont A, Bursell SE, Feener EP. Role of the angiotensin II type 1 receptor in the pathogenesis of diabetic retinopathy: effects of blood pressure control and beyond. J Hypertens. 2006;24:573–580.

Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med. 2009;361:40–51.

Wilkinson-Berka JL, Tan G, Jaworski K, Ninkovic S. Valsartan but not atenolol improves vascular pathology in diabetic ren-2 rat retina. Am J Hypertens. 2007;20:423–430.

Fernandez LA, Twickler J, Mead A. Neovascularization produced by angiotensin II. J Lab Clin Med. 1985;105:141–145.

Aiello LP, Bursell SE, Clermont A, et al. Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective beta-isofom-selective inhibitor. Diabetes. 1997;46:1473–1480.

Funatsu H, Yamashita H, Ikeda T, Nakanishi Y, Kitano S, Hori S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with diabetic macular edema and other retinal disorders. Am J Ophthalmol. 2002;133:537–543.

Funatsu H, Yamashita H, Nakanishi Y, Hori S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with proliferative diabetic retinopathy. Bri J Ophthalmol. 2002;86:311–315.

Schiffman RM, Fisher L, Nussbaum J, Edwards P, Scicli G. Prorenin and its receptors in control and diabetic rat eyes. Invest Ophthalmol Vis Sci. 1992;33:1362.

Pradhan R, Fong D, March C, et al. Angiotensin-converting enzyme inhibition for the treatment of moderate to severe diabetic retinopathy in normotensive type 2 diabetic patients a pilot study. J Diabetes Complications. 2002;16:377–381.

Vaananen A, Vapaatalo H. Local ocular renin. J Hypertens. 1999;17:491–496.

Chaturvedi N, Porta M, Klein R, et al. Direct programme study group. Effect of candesartan on prevention (Direct Prevent 1) and progression in experimental choroidal neovascularization. J Med. 2000;84:i29–i31.

Gragoudas ES, Adams AP, Cunningham ET, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. New Engl J Med. 2004;351:2805–2816.

Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. New Engl J Med. 2006;355:1419–1431.

Praddaue F, Cousins SW, Pecher C, Marin-Castano ME. Angiotensin II induced hypertension regulates AT1 receptor subtypes and extracellular matrix turnover in mouse retinal pigment epithelium. Exp Eye Res. 2009;89:109–118.

Strain WD, Chaturvedi N. The renin-angiotensin-aldosterone system and the eye in diabetes. J Renin Angiotensin Aldosterone Syst. 2002;3:243–246.