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Review

Therapeutic targets of renin-angiotensin system in ocular disorders

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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 database published from 1977 to 2016. The search terms were a renin-angiotensin system, angiotensin, angiotensin receptor, prorenin, pro (renin) receptor, angiotensin converting enzyme inhibitor, angiotensin receptor blocker associated with ocular disorders like cataract, glaucoma, diabetic retinopathy, 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, extracellular signal-regulated kinase, and advanced glycation end products in the ocular tissues and leads to several blinding disorders like diabetic retinopathy, glaucoma, and macular degeneration. The classical and newer RAS inhibitors have illustrated protective effects on blinding disorders, including diabetic retinopathy, 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

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glands,[10] thymus,[11] and ocular tissues.[12] The presence and 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 renin-angiotensin system, angiotensin, angiotensin receptor, prorenin, pro (renin) receptor, angiotensin converting enzyme inhibitor, angiotensin receptor blocker associated with ocular disorders like cataract, glaucoma, diabetic retinopathy, macular degeneration, and uveitis. All article types, including original research article, 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,

Table 1
Distribution of 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	2,14,15,17
Renin	Retina (Muller cells, RPE), iris, vitreous fluid, choroid	Human, rabbit	2,14,18–22
	Ciliary body	Human, rabbit, rat	
	Sclera, cornea	Human	
	Aqueous fluid	Rabbit	
Angiotensinogen	Retina (Muller cells, RPE), ciliary body, vitreous fluid, choroid, iris	Human, rabbit	2,21,22
	Sclera, cornea, conjunctiva	Human	
	Aqueous fluid	Rabbit	
Ang-I	Retina, choroid, subretinal fluid	Porcin	14,16
	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	16,21,23–25
	Ciliary body, aqueous fluid	Human, rabbit	
	Cornea	Human	
	Iris	Rabbit	
Ang (1–7)	Retinal Muller cells, aqueous humor	Human	25,26
ACE	Retina (Muller cells, ganglion cells, retinal vessel endothelial cells, photoreceptor cells), choroid	Human, monkey, dog, rabbit, porcine	2,21,22,24,26–40
	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	25,26,41,42
Chymase	Vitreous fluid	Human	33
(P)RR	Retina (Muller cells, RPE, ganglion cells), choroid, iris, ciliary body, cornea, conjunctiva	Human	2,43,44,132
AT_1R	Retina (Muller cells, amacrine cells, RPE, blood vessels, photoreceptors, ganglion cells), choroid, cornea, ciliary body, iris, conjunctiva	Human	2,20,24,25,45–48
AT_2R	Retina (Muller cells, nuclei of some inner nuclear layer neurons, and ganglion cell nuclei)	Human	9,25
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.

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