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The ocular renin–angiotensin system: A therapeutic target for the treatment of ocular disease

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ABSTRACT

The renin–angiotensin system (RAS) is most well-known for its role in regulation and dysregulation of blood pressure as well as fluid and electrolyte homeostasis. Due to its ability to cause cardiovascular disease, the RAS is the target of a multitude of drugs that antagonize its pathophysiological effects. While the "classical" RAS is a systemic hormonal system, there is an increasing awareness of the existence and functional significance of local RASs in a number of organs, e.g., liver, kidney, heart, lungs, reproductive organs, adipose tissue and adrenal. The eye is one of these organs where a compelling body of evidence has demonstrated the presence of a local RAS. Individual components of the RAS have been shown to be present in many structures of the eye and their potential functional significance in ocular disease states is described. Because the eye is one of the most important and complex organs in the body, this review also discusses the implications of dysregulation of the systemic RAS on the pathogenesis of ocular diseases and how pharmacological manipulation of the RAS might lead to novel or adjunctive therapies for ocular disease states.

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Abbreviations: AGEs, Advanced glycation endproducts; AMD, Age-related macular degeneration; Ang, Angiotensin; ACE, Angiotensin converting enzyme; ARB, Angiotensin receptor blocker; AGT, Angiotensinogen; AT_1R, Angiotensin type 1 receptor; AT_2R, Angiotensin type 2 receptor; AT_4R, Angiotensin type 4 receptor; AC, Anterior chamber; AqH, Aqueous humor; BP, Blood pressure; BiP, Bipolar cells; BRB, Blood retinal barrier; BK, Bradykinin; CCR2, C–C chemokine receptor type 2; CB, Ciliary body; CNVM, Choroidal neovascular membrane; DME, Diabetic macular edema; DM, Diabetes mellitus; DR, Diabetic retinopathy; EIU, Endotoxin induced uveitis; ERG, Electroretinogram; EAU, Experimental autoimmune uveitis; ELM, External limiting membrane; GCL, Ganglion cell layer; Glo-1, Glyoxylase; HRP, Handle region peptide; ILM, Inner limiting membrane; INL, Inner nuclear layer; IPL, Inner plexiform layer; ICAM, Intercellular adhesion molecule; IL, Interleukin; IOP, Intraocular pressure; KO, Knockout; MAC, Major arterial circle; MMP, Matrix metalloproteinase; MCP, Monocyte chemotactic peptide; NO, Nitric oxide; NPCE, Non-pigmented ciliary epithelium; NF, Nuclear factor; NFL, Nerve fiber layer; OIR, Oxygen induced retinopathy; OPP, Ocular perfusion pressure; ONH, Optic nerve head; OPL, Outer plexiform layer; ONL, Outer nuclear layer; POAG, Primary open angle glaucoma; RGC, Retinal ganglion cell; PR, Photoreceptor layer; PKC, Protein kinase C; PC, Posterior chamber; (P)RR, (Pro)renin receptor; PG, Prostaglandin; ROS, Reactive oxygen species; RAS, Renin–angiotensin system; RPE, Retinal pigment epithelium; ROP, Retinopathy of prematurity; SC, Schlemm's canal; SHR, Spontaneously hypertensive rat; TGF, Transforming growth factor; TM, Trabecular meshwork; TNF, Tumor necrosis factor; VEGF, Vascular endothelial growth factor.

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Table 1
Ocular tissues that have been shown to express components of the renin–angiotensin system. Both normal and diseased tissue citations have been used. RAS, renin–angiotensin system; Sp, species; NPCE, non-pigmented ciliary epithelium; AGT, angiotensinogen; ACE, angiotensin-converting enzyme, Ang, angiotensin; H, human; RO, rodent; RA, rabbit; D, dog; M, monkey; P, pig; B, bovine; CH, chicken; C, cat; GP, guinea pig; Ham, hamster; SH, sheep (Vita et al., 1981).

RAS component	Sp	Tears/lacrimal gland	Bulbar conjunctiva	Cornea	Trabecular meshwork	Aqueous humor	Iris	Ciliary body/NPCE	Lens	Vitreous	Optic nerve head	Sclera
Prorenin	HBRO					Deinum et al., 1990; Ikemoto, 1978; Danser et al., 1989	Deinum et al., 1990	Sramek et al., 1988; Danser et al., 1989; Deinum et al., 1990; Wallow et al., 1993; Berka et al., 1995		Danser et al., 1989; Deinum et al., 1990; Wallow et al., 1993		
Renin	RAROHBD M					Ikemoto, 1978; Ramirez et al., 1996	Brandt et al., 1994; Ramirez et al., 1996	Brandt et al., 1994; Berka et al., 1995; Ramirez et al., 1996		Ramirez et al., 1996	Ramirez et al., 1996	
AGT	H RARO		Ramirez et al., 1996	Usui et al., 2008		Ramirez et al., 1996	Ramirez et al., 1996	Sramek et al., 1992; Ramirez et al., 1996		Sramek et al., 1992; Ramirez et al., 1996		
ACE	RAHBPDCHCM RO GP SH	Vita et al., 1981; Immonen et al., 1987; Thorig, 1985; Sharma and Vita, 1983	Savaskan et al., 2004	Neels et al., 1983; Udupa and Rao, 1993; Shiota et al., 1997; Sakaguchi et al., 2002; Savaskan et al., 2004; Sharma et al., 2010	Savaskan et al., 2004	Vita et al., 1981; Weinreb et al., 1985; Aydin et al., 2010; Igic et al., 2001; Shiota et al., 1997	Ferrari-Dileo et al., 1988; Okamura et al., 1992; Ramirez et al., 1996; Shiota et al., 1997; Wheeler-Schilling et al., 2001; Geng et al., 2003	Ramirez et al., 1996; Savaskan et al., 2004; Sramek et al., 1992; Igic and Kojovic, 1980; Geng et al., 2003; Wheeler-Schilling et al., 2001; Luhtala et al., 2009; Ferrari-Dileo et al., 1988; Shiota et al., 1997; Strittmatter et al., 1989; Zrenner, 1989		Ferrari-Dileo et al., 1988; Nakanishi et al., 2002; Maruichi et al., 2004; Ishizaki et al., 2006; Luhtala et al., 2009; Aydin et al., 2010	Ferrari-Dileo et al., 1988; Ramirez et al., 1996; Wheeler-Schilling et al., 2001	Wagner, 1996; Sakaguchi et al., 2002; Shiota et al., 1997
ACE2	P							Luhtala et al., 2009		Luhtala et al., 2009		
Ang I	H P					Igic et al., 2001	Danser et al., 1994; Okamura et al., 1992	Danser et al., 1994		Funatsu, 2002; Bertazolli-Filho et al., 2007		
Ang II	HRAPCH		Ramirez et al., 1996; Savaskan et al., 2004	Savaskan et al., 2004; Usui et al., 2008	Osusky et al., 1994; Savaskan et al., 2004	Danser et al., 1994; Osusky et al., 1994; Ramirez et al., 1996	Okamura et al., 1992; Danser et al., 1994; Senanayake et al., 2007	Danser et al., 1994; Ramirez et al., 1996; Hou and Delamere, 2002; Savaskan et al., 2004; Senanayake et al., 2007; Luhtala et al., 2009		Ramirez et al., 1996; Senanayake et al., 2007; Funatsu, 2002; Maruichi et al., 2004	Ramirez et al., 1996; Savaskan et al., 2004	
Ang 1–7												
Chymase	D M Ham			Sakaguchi et al., 2002				Shiota et al., 1997		Maruichi et al., 2004		Shiota et al., 1997; Sakaguchi et al., 2002
Neurolysin	B RO							Bertazolli-Filho et al., 2007				
Neprilysin	H									Hara et al., 2006		
Prolyloligo-peptidase	B								Sharma and Ortwerth, 1994			