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REVIEW

Ocular renin-angiotensin system with special reference in the anterior part of the eye

Mervi Holappa, Heikki Vapaatalo, Anu Vaajanen

Mervi Holappa, BioMediTech, University of Tampere, 33520 Tampere, Finland

Heikki Vapaatalo, Institute of Biomedicine, Pharmacology, University of Helsinki, 00014 Helsinki, Finland

Anu Vaajanen, Department of Ophthalmology, Tampere University Hospital, 33521 Tampere, Finland

Anu Vaajanen, SILK, Department of Ophthalmology, School of Medicine, University of Tampere, 33521 Tampere, Finland

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Correspondence to: Anu Vaajanen, MD, PhD, Department of Ophthalmology, Tampere University Hospital, P.O. Box 2000, 33521 Tampere, Finland. anu.vaajanen@fimnet.fi
Telephone: +358-3-31164852
Fax: +358-3-31164365

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Abstract

The renin-angiotensin system (RAS) regulates blood pressure (BP) homeostasis, systemic fluid volume and electrolyte balance. The RAS cascade includes over twenty peptidases, close to twenty angiotensin peptides and at least six receptors. Out of these, angiotensin Ⅱ, angiotensin converting enzyme 1 and angiotensin Ⅱ type 1 receptor (Ang Ⅱ-ACE1-AT1R) together with angiotensin (1-7), angiotensin converting enzyme 2 and Mas receptor (Ang(1-7)-ACE2-MasR) are regarded as the main components of RAS. In addition to circulating RAS, local RA-system exists in various organs. Local RA-systems are regarded as tissue-specific regulatory systems accounting for local effects and long term changes in different organs. Many of the central components such as the two main axes of RAS: Ang Ⅱ-ACE1-AT1R and Ang(1-7)-ACE2-MasR, have been identified in the human eye. Furthermore, it has been shown that systemic antihypertensive RAS- inhibiting medications lower intraocular pressure (IOP). These findings suggest the crucial role of RAS not only in the regulation of BP but also in the regulation of IOP, and RAS potentially plays a role in the development of glaucoma and antiglaucomatous drugs.

Key words: Angiotensin converting enzyme 1; Angiotensin converting enzyme 2; Angiotensin converting enzyme-inhibitors; Angiotensin Ⅱ; Angiotensin (1-9); Angiotensin (1-7); Glaucoma; Intraocular pressure; Renin-angiotensin system

Core tip: Many of the central components of renin-

angiotensin system (RAS) have been identified in different structures of the human eye. Recent findings suggest that local RAS accounts for long term changes in ocular tissue level. Antihypertensive drugs which inhibit RAS (Angiotensin converting enzyme or AT-receptor blockade) reduce intraocular pressure suggesting their possibility as anti-glaucomatous drugs in the future. Here we describe the local intraocular RAS especially in the anterior part of eye.

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INTRODUCTION

Glaucoma is after cataract the second leading cause of vision loss worldwide. In 2020, 79.6 million people are estimated to be diagnosed with glaucoma. The majority of these patients are estimated to have open angle glaucoma[1]. Glaucoma is a neurodegenerative disorder that leads to the loss of the axons of the optic nerve and to the death of retinal ganglion cells by non-apoptotic and apoptotic mechanisms all of which in the end cause visual field defects and irreversible vision loss[2-6]. Together with age and family history, increased intraocular pressure (IOP) is one of the known major risk factors for glaucoma[2,6,7]. In subjects with increased IOP, ocular hypotensive medication prevents or delays surgery of glaucoma[8]. A 30% reduction in IOP reduces disease progress 10%-35% in glaucoma patients[9,10]. Even though risk factors and possible outcomes of glaucoma are known, the exact mechanism behind development of glaucoma is still poorly known. Interestingly, imbalances in the local ocular renin-angiotensin system (RAS) cascade have been associated to glaucoma[3].

In addition to the circulating RAS that controls blood pressure (BP) homeostasis, electrolyte balance and systemic fluid volume, tissue-specific RAS, accounting for local effects and long-term changes in tissue level, have been described. Local RA-systems have been demonstrated in different organs studied[11,12], including the human eye[2,12-14]. Systemic antihypertensive drugs which inhibit RAS can reduce IOP. Certain ACE inhibitors[15] and AT1 receptor blockers[16] have been shown to reduce IOP in both non-glaucomatous and glaucomatous patients. In animal studies angiotensin converting enzyme (ACE) inhibitors[17,18], AT1 receptor blockers[19,20], and renin inhibitors[21] have been reported to lower IOP. These findings imply that RAS is not only important in the regulation of BP but that it is possibly also involved in the regulation of IOP[5,22]. However, the question of how RAS is involved in the regulation of IOP remains to be answered.

In this review we describe the tissue RAS cascade and concentrate on the anterior part of the eye. A survey of PubMed using the following keywords was performed to collect the literature on eye, IOP (38214, number of reports), RAS (26697), tissue RAS (4870), angiotensin (110705), angiotensin I (7879), angiotensin Ⅱ (55855), angiotensin converting enzyme (45777), angiotensin (1-9) (28), angiotensin (1-7) (1043), Mas receptor (305), angiotensin receptor (16021), eye disease (4830), glaucoma (55288), diabetic retinopathy (DR) (25958), retinopathy of prematurity (ROP) (5710) and age-related macular degeneration (10875). Combining the used keywords allowed to narrow down the literature to 185 references which were used in this review. They were selected based on the abstracts.

RAS: CIRCULATING RAS AND TISSUE RAS

History

The very first clue of the existence of RAS was found in 1898 when scientists Robert Tigerstedt and Per Bergman in Finland discovered that injecting renal homogenate from one rabbit to another causes an acute elevation of BP indicating that kidney secretes a vasopressor substance, named renin[23,24]. Due to the discovery of this hormone, RAS was first thought to be a hormone system through which the kidney influences systemic cardiovascular regulation[25]. Over 40 years later more RAS effectors were found. In 1940, groups working under Braun-Menéndez and Page reported that previously identified renin catalyzes the formation of pressor peptide, first named angiotonin or hypertensin, from a plasma protein substrate angiotensinogen[22,26,27]. Later angiotonin was renamed angiotensin[22].

In the early 1970s major components of the circulating RAS were found and its important role as a BP and fluid balance regulator was understood[23]. In addition, first antihypertensive medications were developed in the 1970s. First of these drugs was captopril, an ACE inhibitor that was designed to prevent the formation of vasoconstrictive peptide Angiotensin (Ang) Ⅱ[22,23]. In 1988, Ang Ⅱ receptor type 1 blockers (ARBs) were invented which main goal was to prevent the direct effects of Ang Ⅱ mediated through angiotensin Ⅱ type 1 receptor (AT1R)[12]. During past years many new peptides and a new angiotensin reseptor type (Mas receptor, MasR) have been identified. MasR is an important member of the RAS, and its actions are mainly opposite to those of AT1R. Mas-receptors play a role in cell proliferation and antifibrosis as well as vasodilatation and local fluid volume homeostasis. In fact, the potentials of MasR ligands, like Ang (1-7) and ACE2 in degrading vasoconstrictive Ang Ⅱ to vasodilatory peptides are regarded as a present focus of cardiovascular drug development[28-30].

Circulating RAS

When RAS was first described, it was seen as a linear cas-

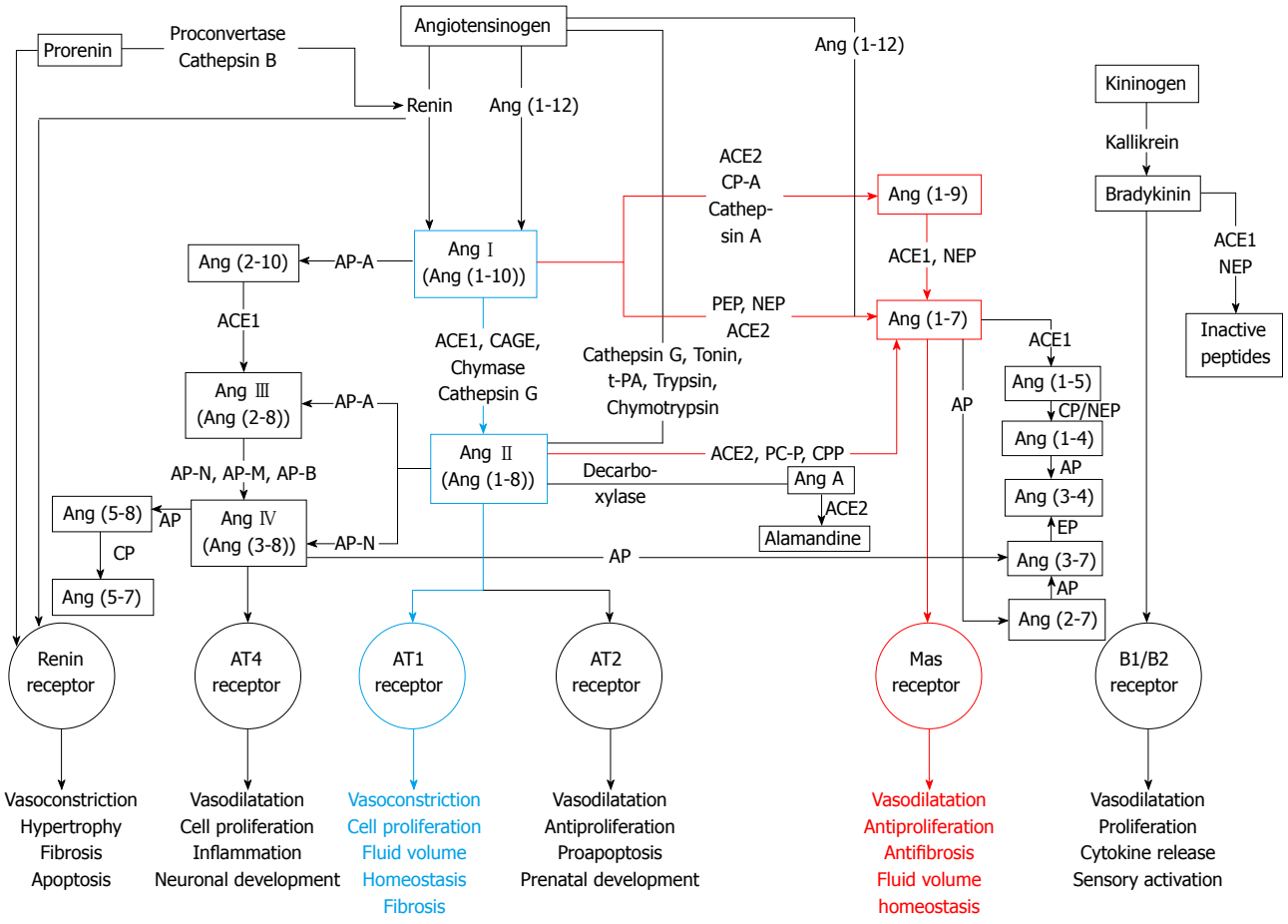

Figure 1 The renin-angiotensin system. The two main pathways of RAS: Ang II-ACE1-AT1R (blue lines) and Ang(1-7)-ACE2-MasR (red lines) are highlighted with colours. ACE(1): Angiotensin-converting enzyme (1); ACE2: Angiotensin-converting enzyme related carboxypeptidase; Ang I, II, III, IV: Angiotensin I, II, III, IV; Ang(1-10): Angiotensin (1-10); Ang(1-8): Angiotensin (1-8); Ang(2-8): Angiotensin (2-8); Ang(3-8): Angiotensin (3-8); Ang(1-9): Angiotensin (1-9); Ang(1-7): Angiotensin (1-7); Ang(1-5): Angiotensin (1-5); Ang(1-4): Angiotensin (1-4); Ang(2-7): Angiotensin (2-7); Ang(3-7): Angiotensin (3-7); Ang(3-4): Angiotensin (3-4); Ang(1-12): Angiotensin (1-12); Ang(5-8): Angiotensin (5-8); Ang(5-7): Angiotensin (5-7); Ang(2-10): Angiotensin (2-10); Ang A: Angiotensin A; AT1R: Angiotensin II type 1 receptor; AT2R: Angiotensin II type 2 receptor; AT4R: Angiotensin II type 4 receptor; AP: Aminopeptidase (-A, -N, -M, -B); B1/B2: Bradykinin receptors; CAGE: Chymostatin-sensitive AngII generating enzyme; CP: Carboxypeptidase; EP: Endopeptidase; Mas receptor: Ang(1-7) receptor type; Nep: Neprilysin; PEP: Prolyl endopeptidase; PCP: Prolylcarboxypeptidase; tPA: Tissue-type plasminogen activator. The picture is updated from Vaajanen *et al*[160].

cade consisting of only one substrate (angiotensinogen), two proteases (renin and ACE1), two peptides (AngI and Ang Ⅱ) and one receptor (AT1R). Today, RAS is known to consist of several enzyme pathways and to include over twenty peptidases, close to twenty angiotensin peptides and at least six receptors[31,32]. Thus, the classical linear cascade has evolved to a cascade with multiple mediators, multifunctional enzymes and multiple different receptors mediating the effects of angiotensin peptides[33-35]. The complexity of the RAS cascade known today is seen in Figure 1.

Central peptides of RAS

Angiotensinogen (AGT) is a 255 amino acids long α-glycoprotein that is synthesized in and released from liver. Renin catalyzes the reaction in which angiotensinogen is converted into AngI[22,36,37]. Mainly synthetized in the liver, angiotensinogen is also formed in heart, vessels, kidney and adipose tissue[38]. The synthesis of α-glycoprotein angiotensinogen is stimulated *e.g.* by inflammation, insulin and estrogens[36].

Angiotensin Ⅰ (Ang Ⅰ), a weak active prohormone, also known as angiotensin (1-10), is a decapeptide generated from angiotensinogen by an enzyme renin[39]. Ang Ⅰ, a weak vasoconstrictor is further cleaved to an octapeptide Ang Ⅱ by ACE1 removing two amino acid residues (His-Leu) from the carboxy terminal of AngI[39,40]. Ang Ⅱ can also be generated by enzymes other than ACE1 such as chymase and cathepsin G.

Angiotensin Ⅱ (Ang Ⅱ), also known as Ang(1-8), first isolated in 1940 and characterized as a potent vasoconstrictor that elevates BP[26,27]. Then, RAS was regarded as an endocrine system in which circulating Ang Ⅱ regulates electrolyte balance, vascular tone, thirst, water intake, aldosterone synthesis, sympathetic activity, sodium handling in the kidney, and antidiuretic vasopressin release from the posterior part of hypophysis[37]. In circulating RAS, renin formed in the kidney is the rate-limiting factor for Ang Ⅱ formation whereas in vascular tissue ACE1 and chymase are the main actors in Ang Ⅱ generation[41].

Ang Ⅱ exerts its main actions *via* two types of

receptors, AT1R and AT2R[36,42]. Ang Ⅱ can be generated from Ang Ⅰ by three different categories of enzymes: ACE1, a metallo dipeptidyl carboxypeptidase, secondly aprotinin-sensitive serine proteases, such as trypsin, tonin, kallikrein and cathepsin G and thirdly a group of chymostatin-sensitive serine proteases, such as human chymase[43]. Ang Ⅱ, a potent vasoconstrictor stimulates the release of vasopressin and aldosterone and thus participates sodium and water retention all of which act in concert to raise BP[37]. ACE inhibitors as antihypertensive medication block the conversion of Ang Ⅰ to Ang Ⅱ by ACE1, thus antagonizing the harmful effects of Ang Ⅱ on AT1R[36].

Angiotensin Ⅲ (AngⅢ), also known as Ang(2-8), is generated from Ang Ⅱ or from angiotensin (2-10) by aminopeptidase A and ACE1[22,23,36,37]. This heptapeptide was found in 1970s and it exerts its actions *via* AT1 and AT2 receptors. AngⅢ has higher affinity to AT2 receptors than to AT1 receptors[44]. AngⅢ induced vasoconstriction and release of aldosterone are close to those of Ang Ⅱ. AngⅢ has 40% of the vasoconstriction activity of Ang Ⅱ[22,23,37]. In some actions on AT1R the role of AngⅢ is at least equally important as that of Ang Ⅱ[23,37].

Angiotensin Ⅳ (AngⅣ), is generated from Ang Ⅱ by aminopeptidase N or from AngⅢ by several other aminopeptidases N, M and B[22,37]. This hexapeptide [Ang(3-8)] exerts its actions *via* angiotensin Ⅱ type 4 receptor (AT4R) found in kidney, lung, brain and heart[23,45,46]. However, AngⅣ can also induce its effects such as renal vasodilatation, hypertrophy and regulation of cell growth in endothelial cells, cardiac fibroblasts and vascular smooth muscle cells by interacting with AT1R[47]. Furthermore, AngⅣ is thought to have an important regulatory role in cardiovascular damage, cognition and renal metabolism and it might be involved in the vascular inflammatory response[22,37].

Angiotensin (1-9) [Ang(1-9)] is formed by cleaving one amino acid residue from the carboxyl terminus of AngI by ACE2[48] and is metabolized by ACE1 and NEP to generate Ang(1-7)[49]. Ang(1-9) can also be generated from Ang Ⅰ through the activity of carboxypeptidase A or cathepsin A[50,51]. The formation of Ang(1-9) is dependent on ACE2 activity[49,52]. The biological function of Ang(1-9) is to increase nitric oxide formation and release of arachidonic acid, enhance bradykinin activity[50] and possibly be involved in the inhibition of platelet function[53]. Ang(1-9) may decrease BP and thus protect the heart and blood vessels and reduce hypertension[54]. Ang(1-9) could mediate its actions *via* the AT2 receptors[54,55].

Angiotensin (1-7) [Ang(1-7)] was originally believed to be an inactive component of RAS. In 1988 this heptapeptide was shown to have actions opposing those of Ang Ⅱ[37]. Ang(1-7) is generated from Ang Ⅱ by ACE2 or by other known peptidases such as prolylendopeptidase and prolyl-carboxipeptidase[23,37,42,56]. Ang(1-7) can also be synthesized directly from AngI by prolylendopeptidase and from Ang(1-9) or from prohormone Ang(1-12) bypassing the synthesis of Ang Ⅱ[37,56]. Furthermore, Ang(1-7) interacts with the kallikrein-kinin system, and can be converted into Ang(1-5) or into Ang (3-7)[22]. Ang(1-7) levels are elevated by ACE inhibitors that increase AngI concentration and on the other hand prevent Ang(1-7) degradation[37].

Ang(1-7) was thought to be devoid of biological functions[37]. Nowadays Ang(1-7) is seen as a protector peptide that counterbalances many functions of Ang Ⅱ by binding to MasR which mediates vasodilating and antiproliferative functions of Ang(1-7)[23,36,55,57]. Although MasR is the main receptor of Ang(1-7), some of the functions may still originate *via* AT1R and AT2R[54,55,57,58]. In addition to the inhibition of Ang Ⅱ-induced vasoconstriction by Ang(1-7), its antiarrhythmogenic, antithrombogenic and growth-inhibitory properties suggest that Ang(1-7) acts as a physiological counterregulator within the RAS, and that Ang(1-7) could be a potential target for drug development[33-35]. In fact, Ang(1-7) has been associated to pathophysiology of several diseases such as. hypertension[59-63], chronic renal diseases[61] and diabetic nephropathy[64,65].

In addition to previously described peptides, RAS cascade includes short peptides which functions and roles in this circulating and tissue-specific regulatory system are still poorly known.

Key enzymes of RAS

Renin, ACE1 and ACE2 are seen as three key enzymes of the RAS. Renin, a specific enzyme having only one known substrate, is an aspartyl protease that cleaves its substrate angiotensinogen to form Ang Ⅰ. Renin cleaves the peptide bond between Leu10 and Val11 at the amino terminus of angiotensinogen. Renin is synthesized as a 406 amino acid residues long inactive prorenin in the juxtaglomerular apparatus of the kidney[22,36,37]. Upon demand synthesized prorenin is cleaved and activated by proconvertase or cathepsin B to generate 340 amino acid residues long catalytically active form of renin. Renin can also be synthesized in organs such as brain, heart, testis, pituitary and adrenal glands, arterial smooth muscle and eye[36]. Classically, renin is secreted by juxtaglomerular cells in response to three different stimuli: (1) decreased arterial BP; (2) decreased sodium levels in the macula densa ultrafiltrate; and (3) increased sympathetic nervous system activity[40,66,67]. Activation of prorenin can be either proteolytic or non-proteolytic. The proteolytic way is irreversible while the latter one is reversible[36].

ACE1 belongs to the M2 family of metallopeptidases containing zinc in its active site. ACE1 is a monomeric glycoprotein that has two different isoforms: somatic ACE1 (sACE1, 150-180 kDa) and germinal ACE1 (gACE1, 90-110 kDa)[36]. The somatic ACE1 is found in various epithelial and endothelial cells[68] whereas germinal ACE1 in germinal cells in the testis[36]. ACE1 is a type I integral membrane protein that consists of hydrophilic C-terminal cytoplasmic domain, hydrophobic transmembrane

domain and a heavily glycosylated N-terminal ectodomain[36]. It is distributed in many tissues and is also found in biological fluids, *e.g.*, in plasma and cerebrospinal fluid[69-71].

ACE1 has an activated water molecule complexed to Zn^{2+} in its active sites[72]. In addition, ACE1 activity depends on the presence of chloride that enhances the binding of different substrates[73]. As an exopeptidase ACE1 cleaves dipeptides from the free C-terminus of Ang Ⅰ and of the hypotensive peptide bradykinin[36,40]. ACE1 can also generate AngⅢ and Ang(1-7) and then further degrade Ang(1-7) to inactive Ang(1-5). Moreover, ACE1 acts in kallikrain-kinin system cleaving bradykinin to inactive compounds[36,40,57]. Because ACE1 participates in regulation of BP and in development of cardiovascular diseases, it is one major target for pharmacotherapy[36].

ACE2, the first known human homologue to ACE1 (42% sequence identity), was cloned in 2000[36,42,48,68,74]. ACE2 was first shown to convert AngI to Ang(1-9)[48]. Later, ACE2 was found to hydrolyze AngⅡ into Ang(1-7) with much higher efficiency (approximately 400-fold) than the hydrolysis of AngI to Ang(1-9)[36,42,49,57,75]. ACE2 is a 805 amino acid residues long (120 kDa) type Ⅰ transmembrane glycoprotein that has been found in organs such as kidney, heart, lungs, liver and brain. ACE2 has a conserved zinc metallopeptidase consensus sequence His-Glu-X-X-His, in wich X stands for any amino acid (HEXXH) in its active site and its activity is regulated by chloride ions[36]. Contrary to ACE1, primarily dipeptidylcarboxypeptidase, ACE2 functions as a monocarboxypeptidase cleaving a single amino acid residue (Phe) from AngⅡ to generate Ang(1-7). Thus, it negatively regulates the activated RAS and ACE1 activity by degrading AngⅡ and increasing Ang(1-7) formation[36,74]. ACE2 is not blocked by conventional ACE inhibitors[58].

ACE2 together with Ang(1-7) and MasR have become the focus of recent research regarding RAS[42,58]. ACE2 is seen as the key player maintaining the balance between the two main pathways of RAS: ACE1-AngⅡ-AT1R and ACE2-Ang(1-7)-MasR[36]. Chronic and long lasting imbalance of these two enzymatic pathways may lead to pathophysiology of the renal, pulmonary, cardiovascular and central nervous system[76].

In addition to previously mentioned enzymes, there are several different peptidases and proteases that act on longer angiotensin peptides thus cleaving them into shorter peptides. For example, AngⅡ can be generated from Ang Ⅰ by four different enzymes: ACE1, CAGE, chymase and cathepsin G[43]. Alternative enzymes acting on different angiotensin peptides are shown in Figure 1.

Alternative pathways for angiotensin II biosynthesis

A number of studies have shown alternative pathways for AngⅡ generation[77-79] being important in physiological and pathophysiological conditions[41,80]. AngⅡ-forming enzymes can be divided into three categories: metallodipeptidyl carboxypeptidase known as ACE1, aprotinin-sensitive serine proteases such as tonin[81], cathepsin G[82], kallikrein[83], trypsin[84] and chymostatin-sensitive serine proteases such as human chymase[85,86] (Figure 1).

Main receptors of RAS

Human (pro)renin receptor [(P)RR] is a 350 amino acid residues long single transmembrane-domain protein containing unglycosylated N-terminal domain responsible for renin and prorenin binding and the short cytoplasmic tail that is involved in the intracellular signalling[36,87]. Compared to the binding of free renin, the binding of renin to (P)RR is 3- to 5-fold more catalytically efficient, thus cleaving AGT to AngI more effectively[36,37].

Four heptahelical G-protein-coupled receptors of RAS: AT1R, AT2R, AT4R and MasR, mediate the effects of angiotensins causing vasodilatation and vasoconstriction[55,88]. AT1 and AT2 receptors are mainly responsible for mediating the effects of AngⅡ, whereas AT4 receptor is target of AngⅣ generated by degradation of AngⅡ[23,37]. A break-down product of Ang(1-7), namely Ang(3-7), can also bind to AT4R. AT4 receptors are located in the brain, lungs, heart, kidneys and liver and they are related to cognitive functions and proliferative effects[43,45,46].

Although AT1 and AT2 subtypes bind Ang Ⅱ in a similar manner, they differ in tissue-specific expression and genomic structure (only about 30% sequence homology) as well as in localization and regulation. AT1 receptors can be activated by Ang Ⅱ but other peptides, such as Ang Ⅲ, Ang Ⅳ and Ang(1-7), can also stimulate AT1R but with lower binding affinity[43]. AT1 and AT2 receptors mediate opposite effects of Ang Ⅱ, the former having negative cardiovascular effects, such as vasoconstriction and aldosterone release, and the latter having positive cardiovascular effects[12]. Whereas the role and function of AT1R is quite well established, the function of AT2R is not as clearly defined[55]. AT2 receptors, which are activated by Ang Ⅱ and also by Ang(1-7), may exert the antiproliferative, proapoptotic, vasodilatory and antihypertensive effects[43,89]. AT2 receptors are known to be involved in differentiation, regulation of growth and regeneration of neuronal tissue, and they are also known to play an important role in prenatal development. AT2 receptors can also inhibit AT1R signaling by directly binding into it. Thus they are considered to be cardiovascular protective receptors[12].

MasR was first discovered in year 1986 by Young *et al*[90] as proto-oncogene. Two years later high MasR levels were reported in the rat central nervous system by the same research group[91]. Later Kitaoka *et al*[92] described MasR expression in the eyes of rhesus macaque. It was early found in the mouse kidney and described as a factor involved in tumorigenesis[93]. Subsequently it is also found in other organs such as in heart, vessels, testis, kidney and brain[94] and very recently in the

human eye[95]. MasR is a G protein coupled receptor that has seven transmembrane domains[93]. This receptor acts antagonistically to the AT1R, mediating number of positive cardiovascular effects, such as vasodilation and antiproliferative effects, of its ligand Ang(1-7)[43]. MasR is part of the counterregulatory arm of RAS (ACE2-Ang(1-7)-MasR) thus balancing the effects of ACE1-Ang Ⅱ-AT1R pathway[34,35].

Tissue RAS

In addition to circulatory RAS, various organs have their own local RA-systems accounting for long-term changes and local effects including proliferation, growth and protein synthesis at tissue level[12,23,41]. The first clues of the existence of local RA-systems came in 1971 when Ganten *et al*[96] demonstrated that RAS components could be produced locally in organs and tissues. This proves that RAS is not only a circulating hormonal system, as thought earlier, but also a tissue-specific regulatory system[23]. Heart, liver, brain, kidney, lungs, intestine and even the human eye have their own local RA-systems[2,12,37].

Local RAS includes all components necessary for independent production of different components of RAS, such as Ang Ⅱ, angiotensinogen, ACE1, AT1R and AT2R[2,12,37]. Thus, RAS is not only an endocrine and circulating, but also a local paracrine and intracrine system regulating more functions than was previously thought[12,41]. Even though many of the local RA-systems operate independently from the circulatory RAS, in heart and kidney, tissue-RAS operates in close interaction with the systemic RAS thus complementing each other's functions[37]. Based on the origin of Ang Ⅱ, local RAS can be divided into extrinsic and intrinsic system, the former getting its Ang Ⅱ from the circulation and the latter obtaining its Ang Ⅱ through local biosynthesis[18].

LOCAL OCULAR RAS

RAS expression

Local RAS has also been identified in the human eye. Researchers have localized all of the central components of RAS, including its receptors, to the structures of the eye in variety of species[2,5]. Moreover, all components of the two main axes of RAS: Ang Ⅱ-ACE1-AT1R and Ang(1-7)-ACE2-MasR have been identified in the ocular structures of different species. When human eye is considered, the components of the two main axes are found in retinal structures and in non-retinal structures of the human eye[2,95,97]. Our research group has very recently succeeded to determine Ang (1-7) and ACE2 in the human aqueous humor[97]. Tables 1 and 2 summarize the localization of RAS peptides and enzymes in non-retinal ocular structures of the human eye. Tables 3 and 4 summarize the localization of RAS receptors in non-retinal ocular structures of the human eye. Although, essential components of RAS haven been identified in the human eye, the importance and functions of intraocular RAS are still unknown. However, intraocular RAS has been the focus of growing interest in recent years due to its possible role in the regulation of IOP through its effects on aqueous humor formation and drainage[5,12]. Furthermore, intraocular RAS activity has been linked to the development of glaucoma through its effect on IOP[2].

Concerning intraocular local RAS, there has been debate whether intraocular angiotensins originate from local production or from the blood compartment[14]. It has been shown that neither Ang Ⅰ, Ang Ⅱ nor angiotensinogen are able to pass the blood-brain barrier which is similar to blood-retina barrier in the eye[14,119,120]. Circulating angiotensins cannot reach the vitreous fluid when blood-retina barrier is intact[14]. However, if disrupted their entering the eye through blood-retina barrier becomes possible[99]. In porcine ocular tissues Ang Ⅰ and Ang Ⅱ levels are 5 to 100-fold over those found from admixture with blood or diffusion from blood[14]. In rabbit and pig ACE1 activity has been shown to be higher in ocular tissues than in plasma[121,122]. The local intraocular RAS is estimated to have a role in the regulation of IOP affecting the formation of aqueous humor and the drainage. It has been shown that systemic antihypertensive RAS-inhibiting medications lower IOP. Certain ACE inhibitors[15] and AT1 receptor blockers[16] have proved to lower IOP in both non-glaucomatous and glaucomatous patients. In animal studies, ACE inhibitors[17,18], AT1 receptor blockers[19,20] and renin inhibitors[21] have been reported to reduce IOP. It has also been suggested that Ang Ⅱ can increase aqueous humor secretion *via* AT1 receptor[118].

Aqueous humour dynamics and IOP

Aqueous humor formation: Intraocular pressure (IOP) can be described as a net sum of homeostatic balance between aqueous humor formation and outflow[123,124]. In the healthy human eye, the flow of aqueous humor against the resistance generates an IOP of about 15 mmHg[125]. Maintaining the optimal physiological IOP is fundamental to keep the optical and refractive properties of the eye, including the right shape of the eye[124,126]. The circulating fluid nourishes unvascularized eye structures such as the cornea and the lens. The normal aqueous humor formation rate is 2.5-2.8 μL/min and the entire volume is replaced every 100 min[5]. This is reduced during sleep, with ageing, and in some systemic diseases like diabetes[127]. Currently IOP is the main risk factor for glaucoma that is amenable to treatment[128].

The ciliary body epithelial is responsible for the production of aqueous humor[123] which is secreted mainly by active ionic transport across the epithelium against a concentration gradient[129]. Active secretion requires energy, produced in hydrolysis of adenosine triphosphate (ATP) by Na^+/K^+ ATPase. Active transport of Na^+ into the posterior chamber by the non-pigmented ciliary epithelial cells induces also water movement from the stromal pool into the posterior chamber. Active transport of Cl^- and HCO_3^- occurs to a lesser extent[130]. In addition to the active secretion two other physiological

Table 1 Renin-angiotensin system components in tears, lacrimal gland, bulbar conjunctiva, cornea, trabecular meshwork, aqueous humor and iris

RAS component	Tears lacrimal gland	Bulbar conjunctiva	Cornea	Trabecular meshwork	Aqueous humor	Iris
Prorenin		White *et al*[98]	White *et al*[98]		Danser *et al*[99]	White *et al*[98]
Renin		White *et al*[98]	White *et al*[98]			White *et al*[98]
AGT		White *et al*[98]	White *et al*[98]		Chowdhury *et al*[100]	White *et al*[98]
ACE1	Vita *et al*[101]	Savaskan *et al*[13]	Savaskan *et al*[13]	Savaskan *et al*[13]	Vita *et al*[101]	Ferrari-Dileo *et al*[106]
	Sharma *et al*[102]				Weinreb *et al*[104]	
	Immonen *et al*[103]	White *et al*[98]	White *et al*[98]		Aydin *et al*[105]	White *et al*[98]
					Holappa *et al*[97]	
ACE2					Holappa *et al*[97]	
Ang I					Danser *et al*[14]	Danser *et al*[14]
						Osusky *et al*[107]
Ang II		Savaskan *et al*[13]	Savaskan *et al*[13]	Osusky *et al*[107]	Danser *et al*[14]	Danser *et al*[14]
				Savaskan *et al*[13]	Osusky *et al*[107]	Senanayake *et al*[108]
Ang(1–7)				Vaajanen *et al*[95]	Holappa *et al*[97]	

Table modified and updated from the table published by Giese et Speth, 2014. ACE1, -2: Angiotensin converting enzyme 1, -2; AGT: Angiotensinogen; Ang Ⅰ, -Ⅱ: Angiotensin Ⅰ, -Ⅱ; Ang(1–7): Angiotensin (1–7); RAS: Renin-angiotensin system.

Table 2 Renin-angiotensin system components in ciliary body, non-pigmented ciliary epithelium, lens, vitreous, optic nerve head and sclera

RAS component	Ciliary body/non-pigmented ciliary epithelium		Lens	Vitreous	Optic nerve head	Sclera
Prorenin	Sramek *et al*[109]	White *et al*[98]		Danser *et al*[99]		White *et al*[98]
	Danser *et al*[99]			Wallow *et al*[110]		
	Wallow *et al*[110]					
	Berka *et al*[111]					
Renin	Berka *et al*[111]	White *et al*[98]				White *et al*[98]
AGT	Sramek *et al*[112]			Sramek *et al*[112]		
ACE1	Igic *et al*[113]	Savaskan *et al*[13]		Ferrari-Dileo *et al*[106]	Ferrari-Dileo *et al*[106]	White *et al*[98]
	Ferrari-Dileo *et al*[106]	White *et al*[98]		Nakanishi *et al*[114]		
	Sramek *et al*[112]			Ishizaki *et al*[115]		
				Aydin *et al*[105]		
ACE2						
Ang I	Danser *et al*[14]					
Ang II	Danser *et al*[14]	Senanayake *et al*[108]		Senanayake *et al*[108]	Savaskan *et al*[13]	
	Savaskan *et al*[13]					
Ang(1–7)	Vaajanen *et al*[95]	Vaajanen *et al*[95]				

Table modified and updated from the table published by Giese et Speth, 2014. ACE1, -2: Angiotensin converting enzyme 1, -2; AGT: Angiotensinogen; Ang Ⅰ, -Ⅱ: Angiotensin Ⅰ, -Ⅱ; Ang(1–7): Angiotensin (1–7); RAS: Renin-angiotensin system.

processes exist in the fluid formation: diffusion from the blood compartment and ultrafiltration. They are passive and require no cellular activity[131]. The whole ciliary body system and its aqueous humor formation should be regarded as a multifunctional and interactive process. Aqueous humor is a mixture of organic solutes, electrolytes, growth factors, cytokines and proteins[132-136]. After the production it is secreted into the posterior chamber from where it flows between the lens and iris into the anterior chamber[132,137,138].

Aqueous humor outflow: *Via* anterior chamber and through the trabecular meshwork and the canal of Schlemm, aqueous humor escapes the eye into the venous blood system[123]. It can leave the eye through three different main routes: the trabecular, the uveoscleral or the uveolymphatic pathways[128]. Trabecular outflow is the main route of drainage accounting for 90% of all aqueous humor outflow, and it is pressure-dependent[5,128,139]. The fluid outflow through the trabecular meshwork is affected by adhesions of trabecular meshwork cells and by the state of the actin cytoskeleton[140].

Outflow, where aqueous humor drains through the ciliary muscle and exits through the supraciliary space and across the anterior or posterior sclera into choroidal vessels, is called the uveoscleral outflow[141] which is independent of IOP and particularly impacted by age[139]. A third outflow route is suggested to exist: channels in the stroma of the ciliary body and interstitial spaces between ciliary muscle bundles. It may function as a backup outflow system[142]. The relevance of this pathway remains to be determined. The other alternative, minor outflow pathways are *via* iris vessels, corneal endothelium, or anterior vitreous body[143].

Pharmacological treatment of glaucoma reduces IOP

Table 3 Renin-angiotensin system receptors in tears, lacrimal gland, bulbar conjunctiva, cornea, trabecular meshwork, aqueous humor and iris

RAS component	Tears lacrimal gland	Bulbar conjunctiva	Cornea	Trabecular meshwork	Aqueous humor	Iris
(P)RR		White *et al*[98]	White *et al*[98]			White *et al*[98]
AT, unknown subtype						Lin *et al*[116]
AT1R						Senanayake *et al*[108]
AT2R						Senanayake *et al*[108]
AT4R						
MasR			Vaajanen *et al*[95]	Vaajanen *et al*[95]		

Table modified and updated from the table published by Giese et Speth, 2014. AT1, 2, 4: Angiotensin Ⅱ type 1, 2, 4 receptor; MasR: Mas receptor; (P)RR: (pro)renin receptor; RAS: Renin-angiotensin system.

Table 4 Renin-angiotensin system receptors in ciliary body, non-pigmented ciliary epithelium, lens, vitreous, optic nerve head and sclera

RAS component	Ciliary body/non-pigmented ciliary epithelium		Lens	Vitreous	Optic nerve head	Sclera
(P)RR	White *et al*[98]					White *et al*[98]
AT, unknown subtype	Lograno *et al*[117] Lin *et al*[116]					
AT1R	Cullinane *et al*[118]	Senanayake *et al*[108]			Senanayake *et al*[108]	
AT2R		Senanayake *et al*[108]			Senanayake *et al*[108]	
AT4R						
MasR		Vaajanen *et al*[95]				

Table modified and updated from the table published by Giese et Speth, 2014. AT1, 2, 4: Angiotensin Ⅱ type 1, 2, 4 receptor; MasR: Mas receptor; (P)RR: (pro)renin receptor; RAS: Renin-angiotensin system.

by decreasing the rate of aqueous humor formation or by increasing the rate of aqueous humor outflow[144].

Glaucoma

It is well-known that defects in the RAS cascade are involved in several cardiovascular and renal diseases, including heart failure, hypertension, ventricular hypertrophy, cardiac remodelling, and chronic renal failure[145-147], but interestingly, imbalances in the RAS cascade are also involved in glaucoma[3], which is a neurodegenerative disorder that leads to the loss of the axons populating the optic nerve and to the death of retinal ganglion cells by non-apoptotic and apoptotic mechanisms[2,3,6]. Together with age and family history, increased IOP is one of the known major risk factors for glaucoma[2,6,7]. Diabetes, migraine/vasospasms and vascular dysfunction are also considered as risk factors for glaucoma development[5,6,128].

Ocular hypotensive medications, laser procedures and surgical means are currently the major therapeutic tools to treat glaucoma[2,6,22]. They all act by lowering IOP thus affecting the onset of the disease[5]. Interestingly, antihypertensive medications acting on RAS have been shown to lower also IOP, suggesting that compounds blocking RAS might be potential anti-glaucomatous drugs in the future[22]. ACE inhibitors can decrease Ang Ⅱ levels in aqueous humor[107]. By reducing blood flow in the ciliary body ACE inhibitors could also decrease aqueous humour production[148]. Furthermore, by preventing the breakdown of bradykinin ACE inhibitors are able to promote synthesis of endogenous prostaglandins, which, as shown with marketed prostaglandin analogues, could increase the uveoscleral outflow thus lowering IOP[149,150]. Biosynthesis of certain matrix metalloproteinases is thought to be associated with increased uveoscleral outflow which leads to relaxation of the ciliary muscle and reduction and compaction of extracellular matrix components within the ciliary muscle, the sclera, the iris and within tissues of the uveoscleral outflow route, all of which might lower IOP by facilitating aqueous humor outflow[151]. ACE-inhibitors activate also the nitric oxide pathway by preventing bradykinin breakdown which increases endothelial nitric oxide formation and causes vasodilatation. Bradykinin stimulates the synthesis of prostaglandins and nitric oxide which also antagonize the vasoconstrictive effects of endothelin-1 and inhibit the overall production of endothelin-1 by endothelial cells. Endothelin 1 is a vasoconstrictive peptide that promotes contraction in the human ophthalmic artery and in the porcine ophthalmic and ciliary arteries[152-154].

Moreover, RAS activity has been described in cultured non-pigmented human ciliary epithelial cells which participate in aqueous humor formation and many of the central components of RAS have been identified in eye structures responsible for aqueous humor formation such as ciliary body[2,116,118]. Ang Ⅱ can activate Ca^{2+} signalling system that increases potassium ion channel activity[155]. Together with cell volume loss, these effects suggest that Ang Ⅱ acts as a operated secretagogue in the non-pigmented ciliary cells[118]. In

addition, Ang Ⅱ activates Na^+/H^+ exchange which leads to an increase in cytoplasmic sodium concentration[129]. In ciliary and renal tubular epithelium sodium handling related mechanisms are common pathogenetic factors. This might explain the coexistence of glaucoma and systemic hypertension[156]. Other explanations have also been suggested for the relationship between hypertension and glaucoma development. Hypertension is shown to cause impairment in autoregulation of the posterior ciliary circulation[157] and suggested to induce microvascular damage thus worsening blood flow to the optic nerve[158]. Furthermore, antihypertensive therapy has been described to cause hypotensive episodes that can injure the optic nerve[159].

In addition to possible role of RAS in the aqueous humor formation, RAS is suggested to act in aqueous humor outflow. Ang Ⅱ is able to promote cell proliferation in bovine trabecular meshwork cells and increase synthesis of collagen *in vitro*. Moreover, intracamerally administered Ang Ⅱ reduces uveoscleral outflow[160]. Paradoxically, natural and synthetic Ang Ⅱ, when administered intravenously, lowered IOP in anaesthetized cats[161].

RAS AND OTHER EYE DISEASES

In addition to glaucoma, local intraocular RAS has been associated with other severe eye diseases that can lead to permanent vision loss, such as age-related macular degeneration (AMD), ROP and DR. Dysregulation of RAS cascade participate in the development of these severe eye diseases.

AMD

In elderly people, AMD is one of the leading causes of visual impairment. Both dry and wet forms of the disease are associated with vision loss. Dry forms of the disease accounting for 90% of the cases lead to the significant decline of photoreceptors which ultimately causes central vision loss. On the contrary, wet form of AMD is characterized with pathological growth of cloroidal blood vessels that will eventually populate retina after breaking through the underlying Bruch's membrane. In addition to old age, environmental factors, smoking, genetic susceptibility and systemic hypertension are regarded as risk factors for developing AMD. Interestingly dysregulation of the RAS cascade is suggested to play a role in the development of AMD[2,162,163].

Three key observations are held as evidence showing the possible involvement of RAS in the development of AMD. Firstly, systemic hypertension is a risk for the development of AMD. Secondly, dysregulation of RAS may have an impact on retinal pigment epithelium function and photoreceptor viability due to the observations that Ang Ⅱ can modulate retinal pigment epithelium. Thirdly, Ang Ⅱ is involved in retinal angiogenesis thus it might have a role in choroidal neovascularisation[2,162]. Animal studies have proven that administered AT1R antagonist (losartan)[164] and other AT1 receptor blockers[165] and (pro)renin receptor inhibitor[166] can reduce choroidal neovascularization thus having a positive effect on AMD.

ROP

ROP is a neovascular disease affecting premature newborns. ROP is associated with pathological retinal neovascularisation that causes complications such as tractional retinal detachment, macula dragging and vitreal haemorrhage, all of which can lead to vision loss[162]. The main risk factors for the disease are low birth weight and lower gestational age, both of which correlate with immaturity of retina at birth. In fact, in industrialized countries, approximately two-thirds of infants with birth weight less than 1.25 kg manifest some degree of retinopathy[167]. The cause of ROP is thought to be the retinal blood vessels expanding from the optic nerve which growth halts when a premature neonate is brought into a high oxygen environment. When the newborn is brought back to normal conditions, the inner vasculature in retina fails to regain normal vessel growth thus creating an avascular area and causing neovascularisation and epiretinal angiogenesis that can lead to vision loss[168].

Studies using animal models have suggested that RAS is involved in the development of ROP. Infants that are diagnosed with ROP have had elevated serum prorenin levels[169], ocular renin levels[170,171] and increased AT1R and AT2R expression[170]. Treating oxygen induced retinopathy in animal models with ACE inhibitors and AT1R antagonists during the normal air conditions reduces pathological angiogenesis on the surface of the retina[170,172-174]. On the contrary, the role of AT2R in retinal vascular pathology and the effects of the use of AT2R antagonists on retinal angiogenesis are still debatable[171,173,175,176].

Diabetic retinopathy

The development of progressive vascular pathology within the inner retina characterizes DR which is among of the leading causes of blindness worldwide[163,177]. Alterations in the blood-retinal barrier, ischemia, dilated capillaries associated with poor retinal perfusion, retinal microaneurysms, loss of pericytes leading to changes in vascular permeability and the release of growth factors which may induce neovascularisation are all implications of DR[178]. DR can occur as non-proliferative DR (NPDR), which corresponds to the early state of the disease, or as more advanced form of the disease: proliferative DR (PDR). In NPDR the breakdown of the blood-retinal barrier and weakened retinal blood vessels lead to the formation of microaneurysms that can leak fluid into retina causing swelling of the macula. In PDR blood vessels can grow into the vitreous and on the surface of the retina[177,179]. Blocking the RAS cascade seems to reduce the incidence and progression of DR suggesting that RAS may be implicated in the pathogenesis of the disease[180-182]. However, more research is required to understand the complex interplay between RAS cascade and DR.

CONCLUSION

Systemic RAS regulates BP homeostasis, body fluid volume and electrolyte balance. An interesting new observation is intraocular, local RAS, especially existed in the eye structures which are involved in aqueous humor dynamics. Human and animal studies have both shown that antihypertensive drugs blocking RAS at any level can reduce IOP suggesting that these kind of compounds may be potential anti-glaucomatous drugs in the future. Furthermore, compounds elevating Ang(1-7) formation, activating Mas receptors and positively affecting ACE2 activity offer new intriguing opportunities for ocular pharmacology in the future. Although IOP represents the major risk factor in glaucoma, reduction of IOP does not always prevent the progression of disease like in low-tension glaucoma, indicating that factors other than elevated IOP are involved in glaucoma progression. Apoptosis of retinal ganglion cells may be the main possible unsolved reason. ACE inhibitors[183], ARBs[184] and Mas-receptor ligands[185] have showed some potential neuroprotective effects, which will stimulate research activity in the future.

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