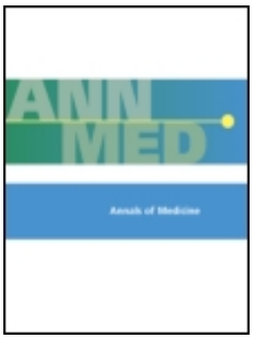

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REVIEW ARTICLE

Does the renin-angiotensin system also regulate intra-ocular pressure?

ANU VAAJANEN[1], SATU LUHTALA[2], OLLI OKSALA[1] & HEIKKI VAPAATALO[1]

[1]*Institute of Biomedicine, Pharmacology, University of Helsinki, Finland, and* [2]*University of Jyväskylä, Department of Biological and Environmental Science, Division of Biotechnology, University of Jyväskylä, Finland*

Abstract
The renin-angiotensin-aldosterone system is known to play an essential role in controlling sodium balance and body fluid volumes, and thus blood pressure. In addition to the circulating system which regulates urgent cardiovascular responses, a tissue-localized renin-angiotensin system (RAS) regulates long-term changes in various organs. Many recognized RAS components have also been identified in the human eye. The highly vasoconstrictive angiotensin II (Ang II) is considered the key peptide in the circulatory RAS. However, the ultimate effect of RAS activation at tissue level is more complex, being based not only on the biological activity of Ang II but also on the activities of other products of angiotensinogen metabolism, often exerting opposite effects to Ang II action. In recent studies, orally administered angiotensin II type 1 receptor blockers and angiotensin-converting enzyme inhibitors lower intra-ocular pressure (IOP), likewise topical application of these compounds, the effect being more prominent in ocular hypertensive eyes. Based on previous findings and our own experimental data, it can strongly be suggested that the RAS not only regulates blood pressure but is also involved in the regulation of IOP.

Key words: *ACE, ACE2, ACE inhibitors, angiotensin II, Ang (1-9), Ang (1-7), eye, glaucoma, intra-ocular pressure, renin-angiotensin system*

Introduction

Open angle glaucoma (OAG) is one of the major causes of vision loss worldwide (1,2). There will be 60.5 million people with glaucoma in 2010, increasing to 79.6 million by 2020, and, of these, 74% will have OAG (3). Among many predictors like age, cup-disc ratio of papilla, thickness of cornea (4), the major known risk factor for glaucoma is increased intra-ocular pressure (IOP), which is a net sum of the homeostatic balance of aqueous humour formation and outflow. A reduction in IOP by 30% reduces disease progression from about 10% to 33%, even in normal tension glaucoma patients (5,6). Ocular hypotensive medication has been shown to prevent the onset of glaucoma in individuals with elevated IOP (7). Current pharmacotherapy comprises of drugs acting on adrenergic α- and β-receptors or on cholinergic muscarine receptors, prostaglandin analgues, and carbonic anhydrase inhibitors. They are administered mainly topically and targeted either to reduce the formation of aqueous humour in the ciliary body or to increase outflow through uveoscleral pathways. Evidence is accumulating to suggest that widely used antihypertensive drugs acting on the renin-angiotensin system (RAS) can also lower IOP. In recent human studies orally administered losartan (angiotensin type 1 receptor blocker (ARB)) (8) and captopril (angiotensin-converting enzyme (ACE) inhibitor) (9) are able to lower IOP in both normotensive and glaucomatous subjects, although blood pressure is reduced in only arterial hypertensive patients. Topical application of olmesartan (ARB) (10,11), ACE (12,13) and renin inhibitors (14) has been reported to lower IOP in animal studies. Topical ACE inhibitors have also been shown to prevent the visual field defect progression in the normotensive glaucoma (15). The effect is more prominent in ocular

Correspondence: Professor Heikki Vapaatalo, Institute of Biomedicine, Pharmacology, PO Box 63, 00014 University of Helsinki, Finland. Fax: +358-9-19125048. E-mail: heikki.vapaatalo@helsinki.fi

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Abbreviations

ACE	angiotensin-converting enzyme
ACE2	angiotensin-converting enzyme-related carboxypeptidase
Ang I,II,III,IV	angiotensin I,II,III,IV
Ang (1-10)	angiotensin (1-10) = Ang I
Ang (1-8)	angiotensin (1-8) = Ang II
Ang (2-8)	angiotensin (2-8) = Ang III
Ang (3-8)	angiotensin (3-8) = Ang IV
Ang (1-9)	angiotensin (1-9)
Ang (1-7)	angiotensin (1-7)
Ang (1-5)	angiotensin (1-5)
Ang (3-7)	angiotensin (3-7)
ARB	angiotensin type 1 receptor blocker
AT1	angiotensin II receptor type 1
AT2	angiotensin II receptor type 2
AT4	angiotensin II receptor type 4
IOP	intra-ocular pressure
Mas receptor	Ang (1-7) receptor type
RAAS	renin-angiotensin-aldosterone system
RAS	renin-angiotensin system

Key messages

- Many recognized renin-angiotensin system (RAS) components have been identified in the human eye.
- Evidence is accumulating to indicate that antihypertensive drugs antagonizing the RAS can also reduce intra-ocular pressure.
- Compounds blocking RAS may prove to be potential antiglaucomatous drugs.
- Our recent findings suggest the potentials of agents which increase angiotensin-converting enzyme-related carboxypeptidase (ACE2) activity and formation of angiotensin (1-7) or activate Mas receptors.

hypertensive animals (10,11). Based on such findings it can strongly be suggested that the RAS not only regulates blood pressure but is also involved in the regulation of IOP. However, the exact mechanism of this action is yet unclear.

In addition to the essential role of circulating RAS and aldosterone (RAAS) in controlling sodium balance, body fluid volumes, and hence blood pressure (16,17), there is a tissue-localized RAS (18,19) which regulates long-term changes in a number of organs. A local RAS has been demonstrated in the vasculature as well as in the adrenal gland, kidney, brain, testis, and ovary (20,21) and also in the eye (22–26). The final effect of RAS activation is complex, being based on the biological activity of angiotensin II (Ang II) and the activities of the other products of angiotensinogen metabolism, often exerting opposite effects on Ang II action (19). In this review we first describe the plasma-localized RAS and then concentrate on the local RAS, especially in the anterior part of the eye.

The renin-angiotensin system: circulating RAS and tissue RAS

History

The scientists Tiegerstedt (Finnish) and Bergman found in 1898 that crude saline extracts from the kidney contained a pressor substance which they named renin. In 1934 Goldblatt and co-workers demonstrated that constriction of the renal arteries produced persistent hypertension in dogs. In 1940 groups under Braun-Menéndez and Page reported that renin was an enzyme acting on a plasma protein substrate to catalyse the formation of the actual pressor material, a peptide, first named hypertensin or angiotonin. Later the pressor substance was renamed angiotensin and the plasma substrate angiotensinogen. In 1958 Gross suggested that the renin-angiotensin system was involved in the regulation of aldosterone secretion in the kidneys. It was found that renin secretion increased with depletion of Na^+. Thus the renin-angiotensin system came to be recognized as a mechanism to stimulating aldosterone synthesis and secretion and an important homeostatic mechanism in the regulation of blood pressure and electrolyte composition. In the 1970s the development of antihypertensive drugs started: first via inhibition of angiotensin II formation (ACE inhibitors) and later via angiotensin II receptor type 1 blocking (16,17).

Circulating RAS

The complexity of the present knowledge of RAS is described in Figure 1. The obligatory substrate of the RAS is angiotensinogen, an α-glycoprotein which is synthesized in and released from the liver and cleaved in the circulation by the enzyme renin secreted from the juxtaglomerular apparatus of the kidney to form the decapeptide angiotensin I (Ang I) (16,18,19). Importantly, renin has an inactive precursor, prorenin. Prorenin is released constitutively from the kidney, its plasma levels are higher than those of renin, and its action on RAS is probably marked not only via renin but also via renin receptor (27). Ang I is a weak vasoconstrictor and is cleaved to the more potent octapeptide Ang II by the ACE, membrane-bound proteinase which is predominantly expressed

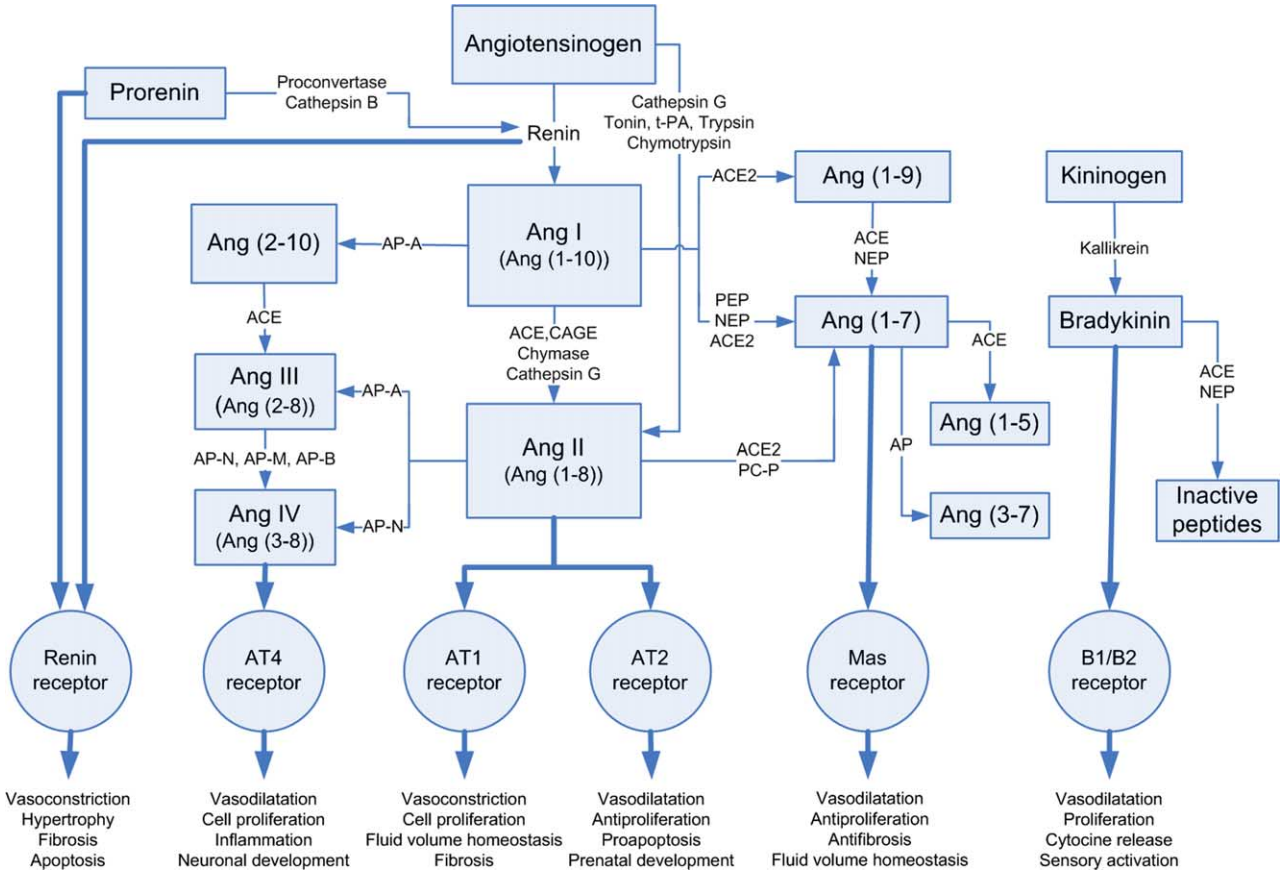

Figure 1. Tissue RAS-angiotensin synthesis pathways. (ACE = angiotensin-converting enzyme; ACE2 = angiotensin-converting enzyme-related carboxypeptidase; Ang I,II,III,IV = angiotensin I,II,III,IV; Ang (1-10) = angiotensin (1-10); Ang (1-8) = angiotensin (1-8); Ang (2-8) = angiotensin (2-8); Ang (3-8) = angiotensin (3-8); Ang (1-9) = angiotensin (1-9); Ang (1-7) = angiotensin (1-7); Ang (1-5) = angiotensin (1-5); Ang (3-7) = angiotensin (3-7); AT1 = angiotensin II type 1 receptor; AT2 = angiotensin II type 2 receptor; AT4 = angiotensin II type 4 receptor; AP = aminopeptidase (-A,-N,-M,-B); B1/B2 = bradykinin receptors; CAGE = chymostatin-sensitive Ang II generating enzyme; Mas receptor = Ang (1-7) receptor type; Nep = neprilysin; PEP = prolyl endopeptidase; PCP = prolylcarboxypeptidase; tPA = tissue-type plasminogen activator.)

in high concentrations on the surface of endothelial cells in the pulmonary circulation (18). ACE is also known as kininase II; it has in addition a catalysing effect on the bradykinin cascade (28) and thus a degrading effect on the highly vasodilatative bradykinin (19).

Angiotensin II (Ang II) is a potent vasoconstrictor and is considered the main effector peptide in the RAS. The mechanism of RAS-induced hypertension has generally been attributed to the direct effects of Ang II on Ang type 1 receptors in vascular smooth muscle and stimulation of the release of aldosterone, a mineralocorticoid from the adrenal cortex (18,19). Ang II elevates blood pressure by releasing noradrenaline from adrenergic nerve endings, endothelin-1 (a potent vasoconstrictor) from the endothelium, and vasopressin (a vasoconstricting pituitary hormone), as well as by reducing baroreceptor activity (29). Additionally, Ang II stimulates free radical production, plasminogen activator inhibitor-1 release, and tissue factor and adhesion molecule expression. Ang II is considered to diminish beneficial effects of nitric oxide by inhibiting nitric oxide synthase. In blood vessels, it stimulates muscle cell proliferation and leukocyte activation (16,19,30). The half-life of Ang II is short, a couple of seconds (31), but its effects appear rapidly and are long-lasting.

Angiotensin III (Ang III) is formed from Ang II by aminopeptidase A. Similarly to Ang II, Ang III is also a vasoconstrictor, albeit less potent (16).

Angiotensin IV (Ang IV) is formed from Ang III or directly from Ang II by aminopeptidase activity. In contrast to Ang II, Ang IV is considered a vasorelaxing agent (16). It also has cell-proliferative properties and may be involved in vascular inflammatory responses (32). The precise mechanism and function of Ang IV is not clear, but its vasodilatatory effect is explained by activation of endothelial nitric oxide synthase (16,19).

Angiotensin (1-9) (Ang (1-9)) is formed from Ang I by angiotensin-converting enzyme-related

carboxypeptidase (ACE2). Ang (1-9) has recently been found, and its function is not yet clear, but it is a strong inhibitor of ACE. It enhances the activation of bradykinin, increases nitric oxide and arachidonic acid release, and is possibly involved in the inhibition of platelet function (19,33).

Angiotensin (1-7) (Ang (1-7)), formed from Ang II by ACE-independent enzymes (19,34–36), is one of the most extensively investigated products of the RAS. It can also be synthesized directly from Ang I or Ang (1-9), bypassing the synthesis of Ang II (35). It is a biologically active heptapeptide with high selectivity. In most situations, Ang (1-7) and Ang II exert opposing actions, suggesting a primary role for Ang (1-7) as a counter-regulatory component for the vascular and proliferative actions of Ang II (37–40). Ang (1-7) promotes release of prostanoids from endothelial and smooth muscle cells, release of nitric oxide, vasorelaxation, inhibition of vascular cell growth, and, less frequently, vasoconstriction (36,41–44). Ang (1-7) also has an important stimulatory interaction with the kallikrein-kinin system, and thus has a vasodilatatory effect. This mechanism is complex, involving receptor activation, inhibition of ACE, and the release of nitric oxide and/or prostaglandins. On the other hand, Ang (1-7) may be part of the endogenous regulators of tissue growth (36).

The effects of angiotensins are exerted through specific heptahelical G-protein-coupled receptors (16,37). Ang II receptors in the cardiovascular system are classically divided into two main subtypes: Ang type 1 (AT1) and 2 (AT2) receptors. In the rat and mouse, AT1 receptors are further divided into two subtypes, AT1a and AT1b (18,37). There is also an AT4 receptor type which is involved especially in cardiovascular pathology (32) and the recently discovered Mas receptor (38). Most of the known biological effects of Ang II are mediated by the AT1 receptors, which are specifically blocked by AT1 receptor antagonists, widely used as antihypertensive drugs, 'sartans'. AT2 receptors are less well characterized but are considered cardiovascular protective receptors which antagonize the effects of Ang II mediated via AT1 receptors. AT2 receptors may exert the antiproliferative, proapoptotic, vasodilatatory, and antihypertensive effects of angiotensins, and evidently have an important role in prenatal development (16,37). The Mas receptor was first found in the mouse kidney and later in other organs, e.g. heart, brain, and vasculature (38,39). Ang (1-7) is considered to be an endogenous ligand for this angiotensin receptor type (38), which is distinct from AT1 and AT2 receptors, and through it mediates a number of the positive cardiovascular effects of Ang (1-7).

Tissue RAS

In addition to the circulatory system there is a tissue-localized RAS (16,18,19) which regulates long-term changes in different organs. There is thus in tissues a system which can further be divided into an extrinsic and intrinsic RAS (13): angiotensin II is derived either from the circulation or from local biosynthesis. In tissues, Ang II production can be catalysed by enzymes other than the classical ACE. These actions are called renin-independent or ACE-independent pathways for Ang II production. Marked species differences in the local Ang II-forming pathways have been reported (45–47). Further, there is an important enzyme, ACE2, which can degrade Ang I and Ang II to form the biologically active Ang (1-7) acting in many respects opposite to Ang II. According to literature these alternative pathways are important both in physiological and pathophysiological conditions (48,49).

Alternative pathways for angiotensin II biosynthesis

Chymostatin-sensitive Ang II generating enzyme (CAGE)-dependent pathway of Ang II production

CAGE is a protease able to convert Ang I to Ang II. It is found e.g. in human, monkey, and dog aorta distributed predominantly in adventitia, while ACE is found localized mainly in the endothelium. The distribution of these enzymes may reflect distinct functional roles (50). The exact role of CAGE in physiology is unknown (19).

Chymase-dependent pathway of Ang II production

Chymases (α- and β-chymase) are chymotrypsin-like serine proteases found in the heart, kidney, vascular smooth muscle, and secretory granules of mast cells (49,51,52). They are able to cleave Ang I to produce Ang II, but not to form Ang II directly from angiotensinogen (51). Chymase-mediated Ang II production may have an important role especially in pathological conditions (49,52). Chymase may be associated with the development of diabetic and hypertensive nephropathy (53), vascular proliferative diseases (54), myocardial infarction (55), and atherosclerosis (56).

Cathepsin G-dependent pathway of Ang II production

Cathepsin G is a serine protease found in the granules of human neutrophil cells. It is able to convert Ang I to Ang II, but can also produce Ang II directly from angiotensinogen (57,58). A serine

protease, called tonin (59), as well as tissue-type plasminogen activator, trypsin, and chymotrypsin are also able to release Ang II directly from angiotensinogen (19,60).

ACE2-dependent pathway of Ang metabolism

The human angiotensin-converting enzyme-related carboxypeptidase (ACE2) is a structurally related homologue of ACE with 42% protein sequence identity (33,61), but it acts contrary to the carboxypeptidases, and increase Ang (1-9) and Ang (1-7) formation. Unlike ACE, ACE2 is not able to degrade bradykinin. ACE2 is mainly expressed in cardiac blood vessels, kidneys, and testis (33,62). It is considered to be a balancing counter-regulator in the RAS, as it is able to cleave especially the bioactive Ang II to form Ang (1-7), and Ang I to form Ang (1-9) (33,63). It is of importance in that both Ang (1-7) and Ang (1-9) have physiological effects opposite to those of Ang II. In the absence of ACE2, the predominant effects of Ang II lead to vasoconstriction and hypertension. In the light of these findings, ACE2 can be regarded as an important modulator of blood pressure (63).

Aqueous humour dynamics and IOP

IOP is maintained by a homeostatic balance of formation and outflow of aqueous humour (AH). AH is produced by the ciliary processes at approximately 2–3 μL/min, and the entire volume is replaced every 90–100 min. There are three essential steps in the formation of AH: the blood circulation must be sufficient in the ciliary processes, the plasma must be filtered into tissue spaces, and the filtrate must pass through the double-layered epithelium to enter the posterior chamber (64). The widely used oculohypotensive drug timolol maleate reduces the formation of AH via β-adrenergic receptor (65), though the exact mechanism here is not known. Carbonic anhydrase inhibitors administered as eye drops or orally also diminish the formation of AH, like the less potent α-adrenergic drugs. AH passes from the posterior chamber through the pupil into the anterior chamber and has several routes to exit from the eye. The main route (90%) of drainage in the normal eye is the route through the trabecular meshwork (66). Uveoscleral outflow constitutes approximately 10% of total outflow, but the potent antiglaucomatous prostaglandin analogues act by this route (67). The other alternative, albeit minor, pathways of outflow are those through iris vessels, corneal endothelium, or anterior vitreous body. Anticholinergics such as pilocarpine probably increase the trabecular outflow by contraction of the ciliary muscle, which leads to changes in the geometry of the trabecular meshwork.

RAS and the eye

RAS expression

Many of the recognized RAS components have already been identified in the human eye (18,22–25), except for the recently described Mas receptor for Ang (1-7) and novel peptidases degrading angiotensins (Table I). Prorenin, the precursor of renin, has been detected in the human non-pigmented ciliary epithelium (68). Renin mRNA has been detected in retinal pigment epithelium (but not in the neural retina) and choroid (24). Angiotensinogen has been found in the non-pigmented ciliary epithelium (23), and its gene expression has been demonstrated in retina and choroid (24,25) and in sclera (24). ACE has been identified mainly in the human non-pigmented ciliary epithelium (25) but also in the retina and choroid. ACE2 is localized in the Müller cells and photoreceptors in the retina (69). In animal studies, active chymase has been detected in the anterior uveal tract, choroid and sclera (70). In human ocular tissues Ang II receptors (predominantly type 1) are most abundant in the retina. AT1 receptors are found in retinal Müller cells and blood vessels (71) and in ganglion cells and the cornea (25). AT2 receptors are also localized in Müller cells, in ganglion cells, as well as in the inner nuclear layer of the retina (71). Ang II has been detected in many human ocular tissues: in the non-pigmented ciliary epithelium, in cells of the cornea, in epithelial cells of the conjunctiva, and in trabecular meshwork cells, as well as in ganglion cells and photoreceptor cells and in the endothelial cells of retinal and choroidal vessels (25). Ang (1-7) has recently been found in the human retina (71).

There has been debate as to the effects of local RAS in the human eye: does intra-ocular angiotensin originate from local production or from the blood compartment (22)? It has been shown that neither Ang I, Ang II, nor angiotensinogen is able to pass the blood-brain barrier (22,72). The blood-retina barrier in the eye is comparable to this (73). If it is intact, circulating angiotensin cannot reach the vitreous fluid (22), while if the barrier is disrupted this becomes possible (74). It is therefore obvious that the levels of angiotensins and other RAS molecules in the eye are too high to have originated from blood-borne peptides. In porcine ocular tissues Ang I and II levels have proved 5- to 100-fold higher

Table I. Localization of the RAS components in intra-ocular tissues of different species. For abbreviations, see text.

RAS molecule	Eye part	Species	References
Prorenin	Retina	Human	Sramek et al. 1988 (68)
	Ciliary body	Human	Danser et al. 1989 (74)
	Vitreous body	Human	
Renin	Retina	Human, rabbit	Danser et al. 1989 (74)
	Ciliary body	Rabbit	Wagner et al. 1996 (24)
	Choroid	Human, rabbit	Ramirez et al. 1996 (76)
	Iris	Rabbit	
	Vitreous body	Human, rabbit	
	Aqueous humour	Rabbit	
Angiotensinogen	Retina	Human, rabbit	Sramek et al. 1992 (23)
	Ciliary body	Human, rabbit	Ramirez et al. 1996 (76)
	Choroid	Human, rabbit	Wagner et al. 1996 (24)
	Iris	Human, rabbit	
	Vitreous body	Human, rabbit	
	Aqueous humour	Rabbit	
ACE1	Retina	Dog, monkey, human, rabbit, porcine	Vita et al. 1981 (98)
	Ciliary body	Human, rabbit, porcine	Weinreb et al. 1985 (99)
	Choroid	Dog, monkey, human, rabbit, porcine	Ramirez et al. 1996 (76)
	Sclera	Dog, monkey	Wagner et al. 1996 (24)
	Iris	Rabbit, porcine	Shiota et al. 1997 (70)
	Cornea	Human	Geng et al. 2003 (75)
	Vitreous body	Dog, monkey, rabbit	Savaskan et al. 2004 (25)
	Aqueous humour	Human, dog, monkey, rabbit	
	Tear fluid	Human, rabbit	
ACE2	Retina	Rodent	Tikellis et al. 2004 (69)
		Human	Senanayake et al. 2007 (71)
Chymase	Choroid	Dog	Shiota et al. 1997 (70)
	Sclera	Dog	Maruichi et al. 2004 (100)
	Vitreous body	Human	
Ang II receptor type 1	Retina	Human	Savaskan et al. 2004 (25)
	Cornea	Human	Senanayake et al. 2007 (71)
Ang II receptor type 2	Retina	Human	Senanayake et al. 2007 (71)
Ang I	Retina	Porcine	Danser et al. 1994 (22)
	Choroid	Porcine	
	Vitreous body	Porcine, human	
	Aqueous humour	Human	
Ang II	Retina	Human, porcine, rabbit	Danser et al. 1994 (22)
	Ciliary body	Human, rabbit	Ramirez et al. 1996 (76)
	Choroid	Porcine, human, rabbit	Savaskan et al. 2004 (25)
	Iris	Rabbit	Senanayake et al. 2007 (71)
	Cornea	Human	
	Vitreous body	Porcine, human, rabbit	
	Aqueous humour	Human, rabbit	
Ang 1-7	Retina	Human	Senanayake et al. 2007 (71)

than could be accounted for by admixture with blood or diffusion from blood (22). Also ACE activity has been shown to be lower in plasma than in ocular tissues in the rabbit and pig (75,76).

Glaucoma

The exact function of the RAS in the eye has not yet been clarified. As mentioned before, RAS activity has been shown in cultured non-pigmented human ciliary epithelial cells, the cells responsible for aqueous humour formation (77,78). Ang II has been reported to activate a Ca^{2+} signalling system which increases potassium ion channel activity and triggers aldosterone production (79). These effects are accompanied by cell volume loss, indicating that Ang II acts as an operated secretagogue in the non-pigmented ciliary cells (77). Ang II has also been found to cause an increase in cytoplasmic sodium concentration due to activation of Na^+/H^+ exchange (80). In point of fact, mechanisms related to sodium handling are common pathogenetic factors in both ciliary and renal tubular epithelia, which may explain the coexistence of glaucoma and systemic hypertension (81).

ACE inhibitors have been shown to lower Ang II levels in aqueous humour (82). ACE inhibitors might decrease the production of aqueous humour by reducing blood flow in the ciliary body (83). On the other hand, ACE inhibitors promote synthesis of

prostaglandins by preventing the breakdown of bradykinin, which in turn could lower IOP by increasing the uveoscleral outflow (84,85). The precise mechanism underlying increased uveoscleral outflow is not known, but there would appear to be associations with increased biosynthesis of certain matrix metalloproteinases. This leads to relaxation of the ciliary muscle and reduction and compaction of extracellular matrix components within the ciliary muscle, the iris, and the sclera, and within tissues of the uveoscleral outflow pathway. All these effects might facilitate aqueous humour outflow and thus lower IOP (86). By preventing bradykinin breakdown, ACE inhibitors activate the nitric oxide pathway and reduce the formation of the vasoconstrictive peptide, endothelin-1. Endothelin-1 has been shown to elicit contraction e.g. in porcine ophthalmic and ciliary arteries and the human ophthalmic artery (87,88).

There is as yet only limited evidence regarding the role of the RAS in aqueous humour outflow, but Ang II has been reported to be able to induce cell proliferation in bovine trabecular meshwork cells and increase the synthesis of collagen *in vitro* (89). It has been reported that Ang II administered intracamerally diminishes uveoscleral outflow (90). On the other hand, synthetic and natural Ang II have been reported to reduce IOP in *in vivo* studies with anaesthetized cats when administered intravenously (91). The same IOP-lowering effect was seen in the enucleated, arterially perfused cat and human eye. The mechanism behind the effect was considered to consist in vasoconstriction of the iris artery.

Our own studies

We evaluated the effects of exogenous angiotensin II and its breakdown metabolite, angiotensin (1-7) on IOP and on aqueous humour dynamics in ocular normotensive rabbits (92). Administered topically these two peptides did not alter IOP in conscious rabbits during 6 hours. However, intravitreally administered Ang (1-7) reduced IOP for 5 hours ($P<0.05$). This effect was abolished by a selective angiotensin (1-7) antagonist A-779, and partially by the selective angiotensin II type 2 receptor antagonist PD 123,319. On the other hand, in our outflow studies conducted by a two-level constant pressure method (93), Ang II reduced outflow facility ($P<0.01$) dose-dependently, while angiotensin (1-7) had no effect. Based on these findings, we propose that Ang (1-7) reduces IOP possibly via the recently described Mas receptors and probably via decrease of production of aqueous humour. Preliminary data indicate that also in rabbits with congenitally elevated IOP the oculohypotensive effect of Ang (1-7) is more pronounced than in normotensive animals (Vaajanen et al., unpublished data). We have also demonstrated very recently the expression of Mas receptor in the rat eye for the first time, but the precise localization is still under investigation (Vaajanen et al., unpublished data).

There are controversial findings on the relationship between high systemic blood pressure and IOP in man. We found a significant relationship between the development of hypertension and IOP in spontaneously hypertensive rats, a widely used animal model of human essential hypertension, during an 8-week follow-up (94). In double transgenic rats harbouring human renin and human angiotensinogen genes, arterial hypertension developed rapidly together with high IOP. In this study antihypertensive treatment with ARB appeared to reduce IOP slightly parallel to a lowering of blood pressure.

Future possibilities for drug treatment of glaucoma

Evidence is now accumulating to indicate that antihypertensive drugs acting on the RAS can also reduce IOP, and compounds blocking RAS may prove to be potential antiglaucomatous drugs in the future. Our recent findings suggest the potentials of agents increasing ACE2 activity and the formation of angiotensin (1-7) or activating Mas receptors. In addition to the oculohypotensive effects of ACE inhibitors and of AT1 receptor antagonists, chymase, an alternative Ang II-generating enzyme, may also influence the regulation of IOP. Intra-ocular chymase injection has resulted in an increase in IOP in rabbits, which effect was attenuated by a specific chymase inhibitor (95). The exact mechanism by which compounds acting on the RAS reduce IOP is not fully understood. In addition to their ocular hypotensive effect, blockade of the ocular RAS may also exert a neuroprotective effect in glaucoma, since angiotensin-induced vasoconstriction of ocular blood vessels has been considered a pathogenic mechanism in optic nerve damage (96). Compounds acting on the RAS may also have a potential in the treatment and prevention of diabetic retinopathy, a leading cause (97) of blindness in people of working age.

Summary

Compounds acting on the RAS may prove to be potential antiglaucomatous drugs. Especially agents increasing ACE2 activity and the formation of angiotensin (1-7) or activating Mas receptors are

new options, in addition to classical ACE inhibitors and Ang II receptor type 1 blockers. However, the nature of the present experimental compounds amplifies significant pharmacokinetic challenges in the penetration to the inner parts of the eye.

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