Retinal Renin-Angiotensin System Modulators: A Recent Implication for Therapy in Glaucomatous Patients

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Abstract

Glaucoma is the ultimate commonly acquired optic neuropathy. It signifies a public health challenge since it causes an irreversible blindness. The single known treatment of the disease is decreasing of intraocular pressure (IOP), which has been revealed to lessen glaucoma progress in a diversity of large proportions of clinical trials. Herein in this literature, we briefly define the optical Renin Angiotensin system (RAS) signaling pathway and define the most essential components, physiological actions of major angiotensin peptides, and the Renin Angiotensin system blockers. And discuss the potential implications of their modulators as a new therapeutic target in glaucoma. The literature has shown that the individual RAS modulators including, Angiotensin converting enzymes 1 (ACE1) inhibitors, Angiotensin converting enzymes 2 (ACE2) Activators, Angiotensin receptor-1 (AT-1) blocker, and renin inhibitors have a potentials role in modulation of aqueous humour homodynamic, by neuroprotection of the retinal ganglion cells (RGC) and acceleration of the aqueous humour outflow. In conclusion, RAS modulators have an imperious role in lowering IOP, these compounds will pave the approach for prospect innovation, improvement, and publicizing of novel drugs to treat glaucoma and therefore, aid save vision for millions of people suffering with this slow progressive optic neuropathy.

1 Introduction

The eye is a sensory organ that mainly captures light and offers the sense of vision, as well as transporting non-visual light data encompassing biological rhythms and neurophysiological actions to the brain¹. There are diverse categories of optical diseases were recognized in a human eye. Most of them arise in the retina, which comprises from epithelium cells (pigmented type), glia, neuron as well as blood vessels². The ocular disease that affect human eye and visual system are including: Age-Related Macular Degeneration ;Bulging Eyes; Color Blindness; Cataracts; Crossed Eyes; Diabetic Macular Edema; CMV Retinitis; Keratoconus; Lazy Eye; Eye Floaters and Eye Flashes; Glaucoma; Retinal Detachment; Eyelid Twitching Low Vision; Ocular Hypertension; and Uveitis³.

Currently, the age associated macular degeneration and diabetic retinopathy, and glaucoma are the most public reasons

of impaired vision in the advanced nations. These diseases can be raised up when the systemic and /or local neuronal and vascular injuries are reached⁴.

Glaucoma is next to cataract as a main reason of blindness globally. It represents an even more public health problem than cataracts as the loss of sight it reasons is permanent⁵. In 2020, 80 million people are predicted to be investigated with glaucoma, which is expected to affect more than 11 million cases of consensual blindness⁶. This amount is probably to be even more owing to the aspect that glaucoma can be asymptomatic for a extended period which makes it problematic to recognize till it is complicated⁷.

Glaucoma reflect a multi-factorial and chronic neuro-degenerative condition, which could be defined via the nonapoptotic and apoptotic loss of retinal ganglion cells (RGC) and the damage of retinal nerve fibers that subsequently result

in a irreversible blindness⁸. The cupping of the optic nerve head (ONH) is the most noticeable changes. The developing of disparate disorders in the eye may lead to declining or blocking the aqueous humour outflow from the iridocorneal angle of the eye⁹. These alterations may result in the optical nerve destruction with weakness in optical function.

Glaucoma can be categorized into an open angle or angle closed glaucoma, dependent on the characteristic of the angle of the anterior chamber. The mechanism of open-angle glaucoma is supposed to be slow-moving withdraw l of aqueous humor over the trabecular meshwork while in closed-angle glaucoma; the trabecular meshwork is blocked by the iris¹⁰.

2 Understanding the pathophysiology of Glaucoma

Although several genetic and biological risk causes have been recognized, such as age, ethnicity, family history, and diabetes¹¹. Indeed, in many cases, glaucoma is accompanying secondarily to different systemic conditions like systemic hypotension, hypertension, diabetes, migraine, and others¹². However, the most important typical reason of the glaucoma is the neurodegeneration of retinal ganglion cells (RGCs) as they leave the eye at the optic nerve head (ONH). This neurodegeneration has diverse and complex mechanisms. One of the most famous mechanisms, which lead to damage in RGCs, are including the following:

2.1 The elevation in the intraocular pressure (IOP)

There are many studies were established to normalize the intraocular pressure. However, there are some glaucomatous patients have normal intraocular pressure (which named as normal tension glaucoma (NTG)^{13, 14}. In which destruction happens to the optic nerve deprived of eye, pressure above the normal level. This situation was complicated the developments of effective antiglaucomatous drugs¹⁵.

Aqueous humor is formed by epithelial cells, specifically the non-pigmented epithelium of the ciliary body before it secreted from a posterior chamber to an anterior chamber then its exit from the eye by the two major pathways; trabecular pathway, and uveoscleral pathway. The flow by trabecular path is achieved by means of trabecular meshwork into Schlemm's canal then to aqueous vein; where the uveoscleral pathway is taken place by ciliary muscle, choroid, sclera, plus episcleral tissues^{16, 17}. The balance between the rate of aqueous humour inflow and output is critical in maintaining the range of IOP. The normal range of the IOP in a human eye is between 12-20 mmHg with daily (24 h) and seasonal changes. Some studies report IOP increases with aging¹⁸. The critical upper limit for normal intraocular pressure is about 20.5 mmHg¹⁰. Aqueous humour is produced by 2-3 µl/min by action of ciliary body and it fully refreshed every 2 minutes¹⁹. There are three critical steps accounting for the production of aqueous humour: there is enough blood flow in the ciliary processes; tissue spaces accept

the filtrate of plasma; and this filtrate should pass through bi-layer of epithelial cells in the posterior chamber²⁰. The main drainage of the aqueous humour from the normal human eye is occur through trabecular meshwork (90%)¹⁰, while the uveoscleral pathway is accountable for only 10% of aqueous humour outflow. By this way, many studies stated the anti-glaucomatous effect of prostaglandin analogues is achieved by enhancing the uveoscleral outflow²¹.

2.2 Morphological Defect in the lamina cribrosa

Additional "mechanical" theory in the pathophysiology of glaucoma is concentrated on the lamina cribrosa²². The lamina cribrosa (LC) is a vital ocular portion on the way of the intraocular axons to the intraorbital²³. The LC is tasked with the conflicting responsibilities to support the structure of ONH by tolerating IOP-related mechanical tension, or local distortion, while also permitting the axons an open pathway to exit the eye²⁴. In addition, the 3D structure of LC trabecular involves the vascular capillaries that feed the axons and cells in the laminar region, so attacking high mechanical strains that may decrease vessel lumen size and blood flow is paramount as well²⁵.

Fig 1: Magnified region of the optic nerve head depicting components of the retina, lamina cribrosa, retinal ganglion cell axons (optic nerve) and retinal vasculature that are impacted by ocular hypertension and glaucomatous optic neuropathy. The figure is updated from Najam A. Sharif²⁵

3 Pharmacological treatment of glaucoma

Pharmacological drugs are the primary and first line of treatment for primary open angle glaucoma. Whereas, Laser techniques (argon laser cyclolaser /trabeculoplasty ablation) or surgical processes (trabeculectomy /filtering /iridotomy surgery) for certifying a sufficient aqueous humour outflow are seen as last choice⁹.

Nowadays, the single presently official management is intended to lowering IOP, the most important risk cause identified to time which harms the optic nerve that spreads visual information to the brain²⁶. The pharmacological treatment is aimed to reduce

and/or control intraocular pressure (IOP) which lead to decreasing the rate of glaucoma progression. A meta-analysis of randomized and highly organized clinical studies in glaucomatous people with high intraocular pressure revealed that the progression of that disease is reduced by 14% by each additional 1 mm Hg of intraocular pressure lowering effect²⁷.

The anti-glaucomatous drugs can decline the intraocular pressure by reduction aqueous influx and/or enhancing aqueous drainage. Drugs, which enhance aqueous drainage, are preferred for the treatment of primary open-angle glaucoma because the main defect associated with this type of glaucoma caused by diminished outflow. At present, the pharmacologic classes of anti-glaucomatous, which has constituted to reduce the production of aqueous humor are (e.g., carbonic anhydrase inhibitors [CAIs: dorzolamide; brinzolamide]; beta-blockers [e.g., timolol]; α 2-adrenergic agonists [e.g. brimonidine]), and agents that encourage AQH outflow through the trabecular meshwork (TM) (e.g., pilocarpine; brimonidine), and the backbone first-line uveoscleral outflow enhancers drugs (e.g., FP-receptor agonists travoprost; latanoprost; tafluprost)²⁸⁻³⁰. Lately, two FDA-approved new drugs, namely netarsudil and latanoprostene. netarsudil blocks rho kinase and norepinephrine transporter--it relaxes the TM and Schlemm's canal (SC) cells (thus assisting AQH to drain via the conventional pathway), and it block Na^+/K^+ -ATPase in the epithelial cells of ciliary thereby inhibiting Aqueous humor formation and lowering IOP³¹, while latanoprostene is a nitric oxide (NO)-donating prostaglandin $\text{F}_{2\alpha}$, NO is an endogenous signaling molecule known for its role as a mediator of smooth muscle relaxation and vasodilation³².

Many studies shown that the treatment with anti-hypertension agents which targeting the RAS be able to furthermore reduce the intraocular pressure (IOP). The precise machinery through which these drugs performing on the renin angiotensin system decrease intraocular pressure is still unclear. Moreover, to a hypotensive outcome of RAS in the eye, the interference with an optical renin angiotensin system may also produces a neuroprotective outcome in glaucoma; since the angiotensin can prompt vasoconstriction in ocular blood vessels, which consequently lead to initiate a destructive effect on the optic nerve³³.

In this review, we briefly define the Renin Angiotensin system (RAS) cascade in eye and define the most vital constituents, physiological activities of major angiotensin peptides, and RAS blockers, and discuss the potential implications of their modulators as a new therapeutic target in glaucoma. This system functions at mutually systemic and tissue planes besides it are one of the supreme essential volume controllers in vertebrates.

4 Ocular Renin-Angiotensin System (RAS) signaling cascades

The fundamental duty of circulating RAS and aldosterone (RAAS) is monitoring volumes of body, sodium balance besides systemic BP³⁴, there is an organ specific RAS that controls long-standing fluctuations in several tissues. A resident renin angiotensin system has been established in the blood vessels in addition to their existence in the adrenal gland, kidney, brain, testis, ovary and eye^{33, 36}. Renin, a proteolytic enzyme mainly secreted through the kidneys, cleaves angiotensinogen to angiotensin I (AngI). AngI is additionally converted by angiotensin-converting enzyme and angiotensin-converting enzyme 2 (ACE/ACE2) to diverse angiotensin cleavage compounds. Among them, angiotensin II (Ang II) is the main effector peptide of the RAS, performing on its target cells primarily via Ang II type 1 receptor (AT1-R)³⁷. The final effect of RAS stimulation is significantly complicated because it founded on the organic activity of Ang II peptide in addition to the actions of the rest peptides of angiotensinogen breakdown which might exerted an contradictory action which differ than that of Angiotensin II. Figure 2 summarized the main RAS components and their pathophysiological effects with possible sites of pharmacological intermediation with RAS activity.

In human, numerous of the documented renin angiotensin system components have previously been known ocular tissue. Prorenin, which is the precursor of renin, has been detecting in the non-pigmented portion of the ciliary body. Renin mRNA has been identified in retinal pigment epithelium and choroids. As well as, angiotensin-converting enzyme has been recognized primarily in the non-pigmented portion of the ciliary body of human eye³⁸. In ophthalmic tissues, most of Angiotensin II receptors (primarily AT-R1) are originate in the retina, AT-R1 are recognized in Muller cells plus blood vasculature of retina, in ganglion cells, iris, ciliary body, conjunctiva, and the cornea²⁵. AT-R2 are similarly plentiful in Muller cells, cells of ganglion, in addition to their documentation in the interior nuclear membrane of the retina^{25, 39}. Ang II has been recognized in the different parts of optical tissue including the non-pigmented portion of the ciliary body, epithelial cells of the conjunctiva, the cornea, ganglion cells, in addition to trabecular meshwork, besides the photoreceptor cells, furthermore their recognition in the cells of blood vessels of retina and choroid⁴⁰.

In a preceding study, Danser et al revealed that the circulatory RAS components, including angiotensinogen, Ang-I, and Ang-II from plasma could not permit into the eye⁴¹, proposing that RAS components in the ocular tissues are synthesized in the ocular tissues. This study is confirmed by Brandt et al after detection the renin mRNA in the eye⁴². These findings suggest that the expression of RAS components in optical organs play a vital role in the ocular pathophysiology. All of these potential signaling pathways (Fig 2) play a significant role in the

manipulation of ocular physiology. The effects of these signaling cascades of the ocular RAS may be modulated with RAS inhibitors such as ACEIs and ACE2, angiotensin II Type 1

receptor blockers (AT1-Rceptor antagonist), and renin inhibitors.

Fig 2: major components of RAS. ACE: angiotensin-converting enzyme (ACE1 and ACE2); angiotensin-; AT1: angiotensin II type 1 receptor; AT2: angiotensin II type 2 receptor

4.1 Ocular impact of Angiotensin-converting Enzyme 1 (ACE1) inhibitors

A retrospective study of prolong administration of ACE inhibitors for management of hypertension reported reduction in visual field loss in patients with normal tension glaucoma. In contrast, this observation was not shown in patients using non-RAS inhibitors for the managing of hypertension⁴⁶.

ACE inhibitors been stated to have helpful role on glaucoma by reducing intraocular pressure, Ocular inhibition of angiotensin-converting Enzyme 1 have been found to decline Angiotensin II concentration in aqueous humour^{47, 48}. Moreover, inhibitors of ACE1 may decline the secretion of aqueous humour through decreasing the current of Ciliary body blood vessels⁴⁹. Equally, ACE1 inhibitors stimulate the production of prostaglandins by interfering with metabolism of bradykinin that consequently might decrease intraocular pressure via enhancing the uveoscleral facilities⁵⁰. The exact machinery concerning improved uveoscleral drainage is unclear, however

it could be associated with elevation of biological synthesis of specific matrix metalloproteinases³³.

By inhibition of bradykinin metabolism, ACE1 inhibitors increase the nitric oxide activity in addition to decrease the development of the peptide vasoconstrictors, endothelin-1. This peptide has been found to bring out shrinkage in the blood arteries of ophthalmic ciliary in human and pigs module. Through inhibiting bradykinin degradation, ACE1 inhibitors correspondingly result in a vasodilatation by means of their actions lead to amplified nitric oxide production by ocular endothelial cells⁵¹.

4.2 Ocular Effect of Angiotensin-converting Enzyme Activators (ACE2 Activators)

Amongst the different documented components of the renin angiotensin system, numerous studies have defined the ocular pathological and physiological implication of the axis formed by angiotensin-converting enzyme 2 (ACE 2), Angiotensin 1–7{Ang (1-7)} and Mas receptor. Ang-(1–7) is produced predominantly

by ACE2 and acts on the G-protein-coupled Mas receptor to bring out its functions⁵².

Moreover, a current study showed that Diminazene aceturate that enhance angiotensin-converting enzyme 2- (ACE2) activity and promote the formation of angiotensin (1-7), are novel options as anti-glaucomatous drugs in addition to traditional ACE inhibitors⁵³. These special effects were mediated, by way of Mas receptor, which might involve in the neuroprotection of the retinal ganglion cells (RGC) and acceleration of the aqueous humour outflow⁵⁴. Furthermore, administration of Diminazene aceturate reduced the entrance of inflammatory cells in each of the anterior and posterior portion and reduced the expression of inflammatory cytokines⁵⁵. Therefore; it is potentially that one or other of these pathways may be correlated to the action of Diminazene in intraocular pressure dropping effects.

4.3 Ocular Effect of Angiotensin II receptor 1 Antagonist (AT 1-antagonist)

While Ang(1-7) peptide and ACE2 stimulation are supposed to have positive properties on intraocular pressure, Angiotensin II peptides has proposed to have negative effects on the human ocular tissues. Ang II enhances cell proliferation in trabecular meshwork and upsurges collagen production in vivo ⁵⁶. Ang II is an endogenous peptide that produces powerful blood vessels constriction and helps to regulate systemic BP by triggering the G protein-coupled AT-R1)³³.

Ocular application of olmesartan (CS-088, AT- R1 antagonist) was in primary Phase II glaucoma clinical trials up to the end of 2008. Previous study reported that CS-088 developed some reduction in the intraocular pressure; however, its effect was inadequate and not create dose-response relationship. Their preclinical studies encourage the clinical results. The one-sided laser-induced ocular hypertensive monkeys module treated every 12 hr with a topical olmesartan solution at different doses was produced 15-20 % decreasing in intraocular pressure, after five days of the study⁵⁷. The small reductions in the values of intraocular pressure were elucidated by over counting action through the trabecular and uveoscleral drainage ways. A previous study exposed that candesartan, an Ang II-R antagonist, protected rat retinal neurons from ischemia-reperfusion injury, but the exact mechanisms are still unidentified⁵⁸.

More recent study showed that the orally active AT1-R antagonist candesartan suppressed TLR4 and lipopolysaccharide (LPS)-induced inducible nitric oxide synthase (iNOS) expressions in the EAAC1 KO mouse retina. These results proposed that the RAS is complicated in the innate immune reactions in each of the neural and glial cells, which enhance neural cell death⁵⁹. Moreover, Harry A. et al revealed that losartan (AT-R1 antagonist) treatment significantly, protect RGCs, and modifies scleral remodeling in

glaucomatous mouse module, proposing that the neuroprotective effect of losartan in mouse glaucoma is concomitant with adaptive variations in the sclera expressed at the optic nerve head, and suggesting that this drug may be a good drug-repurposing candidate for glaucoma treatment⁶⁰.

4.4 Ocular effect of renin inhibitors

Renin is the circulating enzyme that converts the angiotensinogen, in the plasma to yield the decapeptide angiotensin 1. Ang 1 have weak vasoconstrictor action and it is fragmented by angiotensin-converting enzyme (ACE) to the more potent octapeptide Ang II^{25,26}.

In a recent study, the topical application of renin inhibitor (ssp 635) was produced significant decrease in the IOP in the laser-induced glaucomatous monkey eyes. This renin inhibitor was created its effect in dose dependent design. The maximum extant and duration of decrease in the IOP was made by highest concentration⁶¹.

Aliskiren exemplifies the first in a new class of renin inhibitors, with the approved promising target for treatment of systemic hypertension and associated cardiovascular disorders. it is considered as a strong and selective inhibitor of renin at subnanomolar levels⁶². Topical aliskiren was found to decline the IOP, which induce by water overloading within a definite intervals of time. Such action was found to be dose-dependent when compare with that shown in the control group at the same parallel period⁶³. These studies suggested that rennin inhibitors, are a novel modulators of RAS signaling cascade which might have an important role for the management of glaucoma. The exact mechanism by which renin inhibitor producing their effect was still unclear, but it expected to be interfere with ocular blood flow, the venous pressure of episcleral vein, and outflow of aqueous humour⁶¹.

5 Conclusion

In addition to the systematic component of renin angiotensin system, which is complicated in controlling of blood pressure and inflammation, there are tissue specific renin angiotensin system has been locally recognized in numerous tissues of the human body, including the eye. It has been identified in several portions of the eye even in that complicated in aqueous humour production and drainage. Due to their excellent efficiency and safety profile, RAS modulators may be novel candidates in aqueous humour dynamics and consequently intraocular pressure controlling. The present review describes individual RAS modulators including, Angiotensin converting enzymes 1(ACE1) inhibitors, Angiotensin converting enzymes 2 (ACE2) Activators, Angiotensin receptor-1 (AT-1) blocker, and renin inhibitors. RAS modulators may have a potentials role in regulation of aqueous humour homodynamic by neuroprotection of the retinal ganglion cells and acceleration of the aqueous humour outflow. In conclusion, RAS modulators have an

imperious role in lowering IOP, these compounds will pave the approach for future innovation, improvement, and publicizing of new therapeutically target to treat glaucoma and therefore aid save vision for millions of people suffering with such a slow progressive optic neuropathic disease.

6 Conflict of interest

None

7 Author's contributions

WSA, ZA and AH carried out the literature review and draft the manuscript. WSA participated in the data collection and arranged in tabular form. All authors read and approved the final manuscript.

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