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UTILIZATION OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS FOR GLAUCOMA

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UTILIZATION OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS FOR GLAUCOMA

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ABSTRACT

Glaucoma is a crucial ocular health issue that warrants meticulous attention according to its status as the leading cause of irreversible visual impairment on a global scale. The incidence of this illness has been on a steady rise, notably within the Asian region. Blood pressure impacts both intraocular pressure (IOP) and ocular perfusion pressure (OPP), which is the pressure responsible for facilitating blood flow to the eyeball. Hypertension is considered a contributing factor in the development of glaucoma. The Renin-Angiotensin-Aldosterone System (RAAS) plays a crucial role in the pathophysiology of hypertension and also contributes to the pathogenesis of glaucoma. The presence of Renin-angiotensin-aldosterone system (RAAS) inhibitors medications, such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) have demonstrated efficacy in reducing intraocular pressure (IOP) and reducing ganglion cell apoptosis. Consequently, these pharmacological agents present a viable therapeutic approach to patients afflicted with hypertension and glaucoma.

Keywords: *Glaucoma; RAAS; Hypertension*

ABSTRAK

Glaukoma merupakan masalah kesehatan mata yang penting karena menjadi penyebab utama gangguan penglihatan permanen di dunia. Angka kejadian penyakit ini terus meningkat, terutama di Asia. Tekanan darah (TD) dapat mempengaruhi tekanan intraokular (IOP) dan tekanan perfusi okular (OPP), yaitu tekanan yang bertanggung jawab untuk memperlancar aliran darah ke bola mata. Hipertensi dianggap sebagai faktor yang berkontribusi terhadap perkembangan glaukoma. Sistem Renin-Angiotensin-Aldosteron (RAAS) memainkan peran penting dalam patofisiologi hipertensi dan juga berkontribusi terhadap patogenesis glaukoma. Kehadiran obat penghambat sistem Renin-angiotensin-aldosteron (RAAS), seperti angiotensin-

converting enzyme inhibitors (ACE-I) dan angiotensin receptor blockers (ARB) memiliki efek positif dalam mengurangi tekanan intraokular (IOP) dan mengurangi apoptosis sel ganglion..
Kata kunci: Glaukoma, RAAS, Hipertensi

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INTRODUCTION

Glaucoma, a crucial ocular health issue, warrants significant attention due to its status as the primary etiology of irreversible blindness worldwide. The incidence of individuals afflicted by this ailment continues to grow annually, particularly in Asia.[1,2] Glaucoma is classified into two types, open-angle and closed-angle, and is associated with several risk factors, including advanced age, gender, familial predisposition, race, myopia, hypertension, diabetes, smoking, and a history of using medications that elevate intraocular pressure (IOP).[3]

Glaucoma and Hypertension

Glaucoma is a form of optic neuropathy that is characterized by damage to the optic nerve and the presence of visual field abnormalities. This condition is typically associated with an elevation in intraocular pressure (IOP).[4,5] The development of glaucoma can be influenced by blood pressure. Hypertension has been observed to potentially decrease the likelihood of glaucoma in individuals under the age of 65, while conversely, it may elevate the susceptibility to glaucoma, particularly open-angle glaucoma (OAG), in older patients.4

Blood pressure has an influence on both intraocular pressure (IOP) and ocular perfusion pressure (OPP). IOP refers to the pressure exerted by the ocular contents on the inner wall of the eye.6 The equilibrium of IOP is maintained through the processes involving the generation of aqueous humor and its outflow via the uveoscleral and trabecular pathways. Elevated IOP results in an excessive strain on the lamina cribrosa, leading to compression, deformation, and subsequent remodeling processes that result in negative impacts on the axons of retinal ganglion cells,

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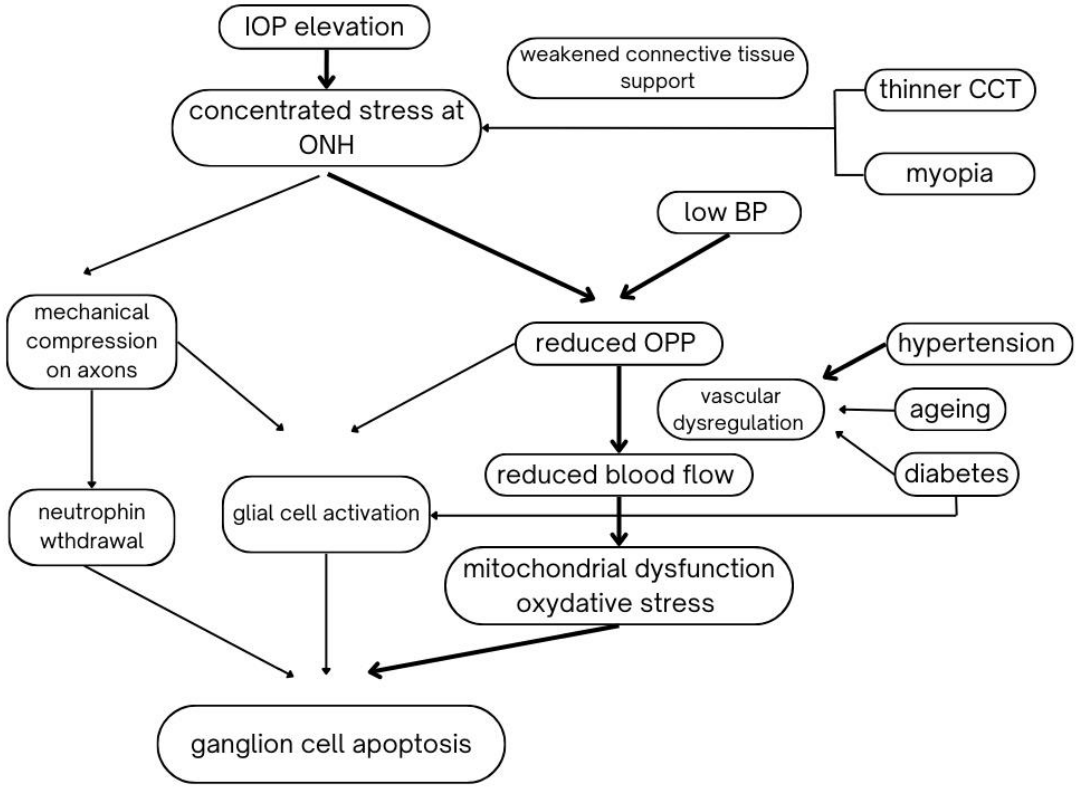

Figure 1. Relationship between Blood Pressure and Ganglion Cell Apoptosis.[7]

ultimately prompting the onset of glaucoma.[4,6] According to Xu8, there exists a significant correlation between blood pressure and IOP among patients who do not use glaucoma medication.

Patients diagnosed with systemic hypertension exhibit an around twofold increase in the likelihood of developing glaucoma in comparison to individuals without hypertension.[6] There is a potential increase in IOP of approximately 0.3 mmHg with a 10 mmHg increase in systolic blood pressure and approximately 0.2 mmHg with a 5 mmHg increase in diastolic blood pressure.[9] Hypertension has been observed to elevate IOP by two distinct mechanisms: (1) elevation of capillary pressure within the ciliary body, and (2) obstruction to the outflow of aqueous humor by increasing episcleral venous pressure.[6,9,10]

Blood pressure and IOP have an impact on ocular perfusion pressure (OPP), which is the pressure that drives blood flow to the eyeball.[11] OPP is calculated as follows: (diastolic blood pressure + 1/3 systolic blood pressure) - IOP.4 Low OPP results from low blood pressure along with high IOP. Low OPP causes the Optic Nerve Head (ONH) perfusion pressure to drop,

which allows ischemia to happen and cause ganglion cell damage and atrophy.[7,11–13]

According to the OPP formula, hypertension is possibly protective against ischemia of the optic nerve, and in fact, this benefit was observed in younger patients.[6,12,13] Chronic hypertension in elderly results in arteriosclerosis, alterations in capillary diameter, and reduced perfusion, all of which impair nutritional and oxygen intake. Additionally, ONH blood pressure autoregulation is disrupted, negating the positive effects of hypertension on OPP.[11,13]

Renin-Angiotensin-Aldosteron System (RAAS)

One system that regulates blood pressure is the renin-angiotensin-aldosterone system (RAAS). RAAS is composed of three primary components: renin, angiotensin II, and aldosterone. The arterial pressure is increased by three components when there is a decrease in renal blood pressure. This is achieved through vasoconstriction, sodium retention, aldosterone secretion, enhanced sympathetic response from the central nervous system, and generation of vasopressin from the hypothalamus.[14]

The RAAS begins with the generation of angiotensinogen, a protein that is synthesized and released by the liver. Renin, released by the kidneys, facilitates the conversion of angiotensinogen into angiotensin I. Angiotensin I under-goes conversion mediated by Angiotensin-Converting Enzyme (ACE) to form Angiotensin II, which serves as the primary mediator of the physiological effects associated with the RAAS.[14,15] Furthermore, Angiotensin II influencesinfluences various organs and elicits a response from the adrenal cortex, leading to the secretion of aldosterone. Aldosterone has the capability to induce the generation of Reactive Oxygen Species (ROS) via the NADPH oxidase pathway. The induction of cell death by ROS can occur as a result of ischemia, which is caused by oxidative stress. Retinal ganglion cells have been observed to undergo injury within a period of seven days following an ischemic event.[16,17]

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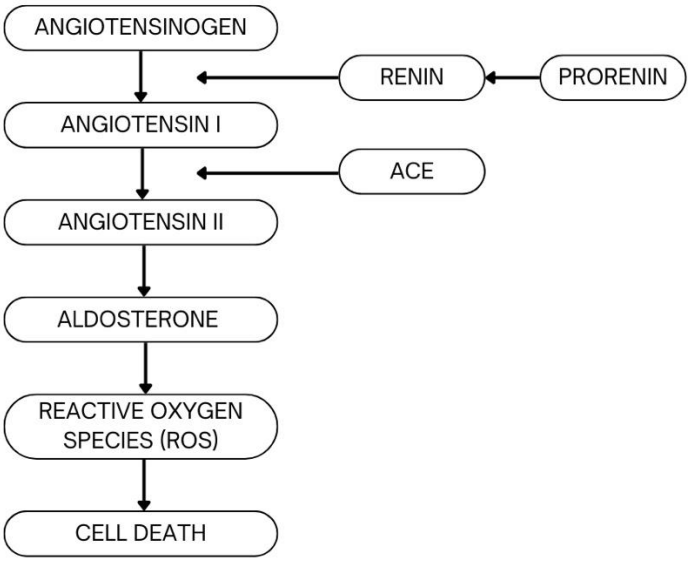

Figure 2. Cell death by RAAS[16]

Table 1. RAS Component Found on the Eye.[18–20]

RAS COMPONENT	LOCALIZATION
Prorenin	Retina, choroid, vitreous body, ciliary body, iris, cornea, sclera, conjunctiva
Renin	Retina, choroid, vitreous body, ciliary body, cornea, sclera
Angiotensinogen	Retina, choroid, vitreous body, ciliary body, iris, cornea, sclera, conjunctiva
ACE1	Retina, choroid, ciliary body, iris, aqueous humour, cornea, sclera, conjunctiva, tear drop
ACE2	Retina
AT_1R	Retina, choroid, ciliary body, iris, cornea, conjunctiva
AT_2R	Retina
Angiotensin I	Vitreous body, aqueous humour
Angiotensin II	Retina, choroid, vitreous body, ciliary body, aqueous humour, cornea

The eye contains components of the RAAS system. The primary pathogenic component of the eye, angiotensin II, is present in the human retina, vitreous body, ciliary body, aqueous humour, cornea, and iris.[18] Angiotensin II, ACE, and Angiotensin II type 1 Receptor (AT1R), also known as Angiotensin II activation receptors in tissues, are present in ciliary bodies and ganglion cells, which are crucial parts of the glaucoma pathophysiology. Angiotensin II has the effect of constricting retinal arterioles, reducing capillary blood flow, promoting neovascularization, increasing collagen production, reducing uveoscleral flow, increasing potassium channel activity thereby increasing sodium concentration in the blood, and triggering cell apoptosis. These effects, together with autoregulation abnormalities of the ciliary circulation, impaired blood flow and direct pressure on the ONH may increase the risk of glaucoma.[18,21]

ACE can break down bradykinin into inactive components. Bradykinin is a component that can stimulate prostaglandin production and has a neuroprotective benefit on the optic nerve.[22]

Anti-RAAS as an Anti-Hypertensive Agent for Glaucoma Patients

RAAS inhibitors, such as ACE inhibitors (ACE-I) and ARBs, may offer a potential treatment option for glaucoma, particularly in glaucoma patients who have hypertension as a risk factor. These inhibitors can increase the flow of aqueous humor, leading to a reduction in intraocular pressure (IOP).[19]

ACE-I affect IOP by influencing the movement of aqueous humor. Specifically, they increase uveoscleral flow by boosting the production of prostaglandins and inhibiting the breakdown of bradykinin. Additionally, they decrease the formation of aqueous humor by reducing blood flow to the ciliary body. The use of ACE-I can decrease the breakdown of bradykinin, which in turn can inhibit the production of reactive oxygen species (ROS) and protect against ischemia in retinal ganglion cells.[20–24] Enalaprilat, an ACE-I, has the ability to decrease by 20%. It is considered the most effective ACE-I when compared to other ACE-Is like ramiprilat and fosinopril.[23,24]

Quigley[25] and Costagliola26 discovered that the utilization of the ARB losartan effectively reduced retinal ganglion cells death by affecting the response of the sclera.[21,25] This was achieved by reducing the production of fibrin and increasing the flow of aqueous humor through the uveoscleral pathway. Hazlewood[27] conducted a comparison of the ARBs losartan, irbesartan and telmisartan. The study revealed that telmisartan and irbesartan have the ability to decrease IOP and telmisartan can increase the outflow of aqueous humor by reducing the production of TGFβ. Irbesartan reduces IOP by around 15%, telmisartan reduces IOP by approximately 13%, and losartan reduces IOP by approximately 20%.[26,27]

The AT1R antagonist CS-088 has the ability to decrease IOP by approximately 5 mmHg. Additionally, it provides a protective effect by inhibiting apoptosis in the eyes of animals afflicted with glaucoma.[28]

Yang[17] and Semba[29] reported that candesartan does not exhibit the potential to decrease intraocular pressure (IOP). However, it does exhibit neuroprotective properties in glaucoma by preventing the death of retinal ganglion cells. This is achieved by lowering the reactivity of AT1R in the retinal ganglion cell layer. Lorenzo-Soler[30] discovered that topically applying candesartan and irbesartan resulted in a reduction in intraocular pressure (IOP) by around 5 mmHg.

CONCLUSION

RAAS has an important role in the pathophysiology of hypertension and has a

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role in the pathophysiology of glaucoma. Hypertension itself is a risk factor for the development of glaucoma. The use of anti-RAAS such as ACE-I and ARB, has been proven to have a beneficial effect by reducing IOP and acting as neuroprotective agent against ONH. Consequently, ACE-I and ARB can be regarded as a viable therapeutic choice for hypertensive patients with glaucoma.

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