

Cardio and neuro protection by renin angiotensin aldosterone system-focus inhibition angiotensin converting enzyme: A systematic review

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Abstract. One of the incidences of cardiovascular disease is stroke, which is a disease that occurs due to impaired brain function caused by damage to cerebral blood circulation. The presence of risk factors for hyperglycemia or hypertension can result in endothelial nitric oxide (eNOS) dysfunction, thereby causing oxidative stress and vasoconstriction of blood vessels. The renin angiotensin system is involved in the physiopathology of stroke and has an important impact on hypertension. This article targets the role of the renin angiotensin system specifically the inhibition of the angiotensin converting system in cardioprotection and neuroprotection. The mechanism of action of the renin-angiotensin-aldosterone system (RAAS) is observed through effects on AT₁, AT₂ and Mass receptors. The future relationship of cardiovascular disease and the renin-angiotensin system is full of possibilities, as new agonist molecules emerge as potential candidates to limit the impairments caused by cardiovascular disease.

1 Introduction

Cardiovascular disease (CVD) is a term for disorders affecting the heart and blood vessels, including coronary heart disease, cerebrovascular disease, hypertension, and peripheral vascular disease [1]. The Global Burden of Cardiovascular Disease found that there were 271 million cardiovascular disease events in 1990, and almost doubled to 523 million events in 2019 [2].

Cardiovascular disease, one of which is stroke, is a disease that occurs due to impaired brain function caused by cerebral circulatory damage [3]. The renal angiotensin Aldosterone System (RAAS) plays a major role in the pathogenesis of cardiovascular disease. Angiotensin Converting Enzyme (ACE) is the most important component within the RAAS. ACE converts angiotensin I (Ang I) into angiotensin II (Ang II) which is the main vasoactive peptide of the RAAS [1]. At the end of process, angiotensin II will act on suprarenal cortex

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which releases aldosterone. Aldosterone is a potent vasoconstrictor that can cause increased sodium reabsorption by the distal tubules and increase extravascular fluid thereby increasing blood pressure [4].

The RAAS, particularly angiotensin II, plays an important role in haemodynamic changes in the kidney. Angiotensin II can increase renal sodium reabsorption by affecting the proximal tubule and through stimulation of aldosterone secretion. Angiotensin II interacts with two specific receptors, angiotensin II type 1 receptor (AT₁R) and angiotensin II type 2 receptor (AT₂R) [5]. High glucose levels in the blood are associated with increased expression of Transforming Growth Factor β (TGF- β) and increased extracellular matrix production. TGF- β is closely associated with RAAS activation [5]. TGF- β plays an important role in myocardial fibrosis by inducing angiotensin II-mediated collagen production and secretion. Overexpression of TGF- β may contribute to the pathogenesis of fibrosis resulting in remodelling or cardiac hypertrophy which ultimately leads to heart failure. RAAS antagonists such as ACE inhibitors and angiotensin receptor blockers can attenuate fibrotic changes mediated by TGF- β [6]. Our study in line with sustainable development goals (SDGs) 3 which aspires to ensure health and well-being for all, including the prevention of diabetic complication such as cardiovascular disease by inhibiting ACE.

2 Material and Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct this systematic review. All references were managed in Mendeley. We searched PubMed and ScienceDirect for articles published in the last 15 years (2009-2024). Our search was done between April and May 2024. The date our last search is the 07 May 2024. The following search term, as free text, we used: cardioprotective AND neuroprotective OR cerebroprotective AND stroke AND inhibition ACE OR renin angiotensin OR renin angiotensin aldosterone.

Inclusion and Eligible Criteria

To find pertinent research examining the impact of ACE inhibition on cardiovascular and neuroprotection, we employed certain inclusion and eligibility criteria in this systematic review. The selected studies were original research article publish in English and within last 15 years (2009-2024), design clinical trial, or randomized control trial and focus on discussing cardioprotective or neuroprotective through the angiotensin converting enzyme inhibition pathway.

Exclusion Criteria

We exclude articles that focused only on the systematic effects of angiotensin without any mention of cardiovascular or cerebrovascular system. After screening, duplicate removals and exclusions, we identified 11 articles that we included into our review (Figure 1).

3 Results and Discussion

After the initial search 74 articles were found on ScienceDirect and 253 articles on PubMed and only 11 articles were selected. The search and screening are represented in Figure 1.

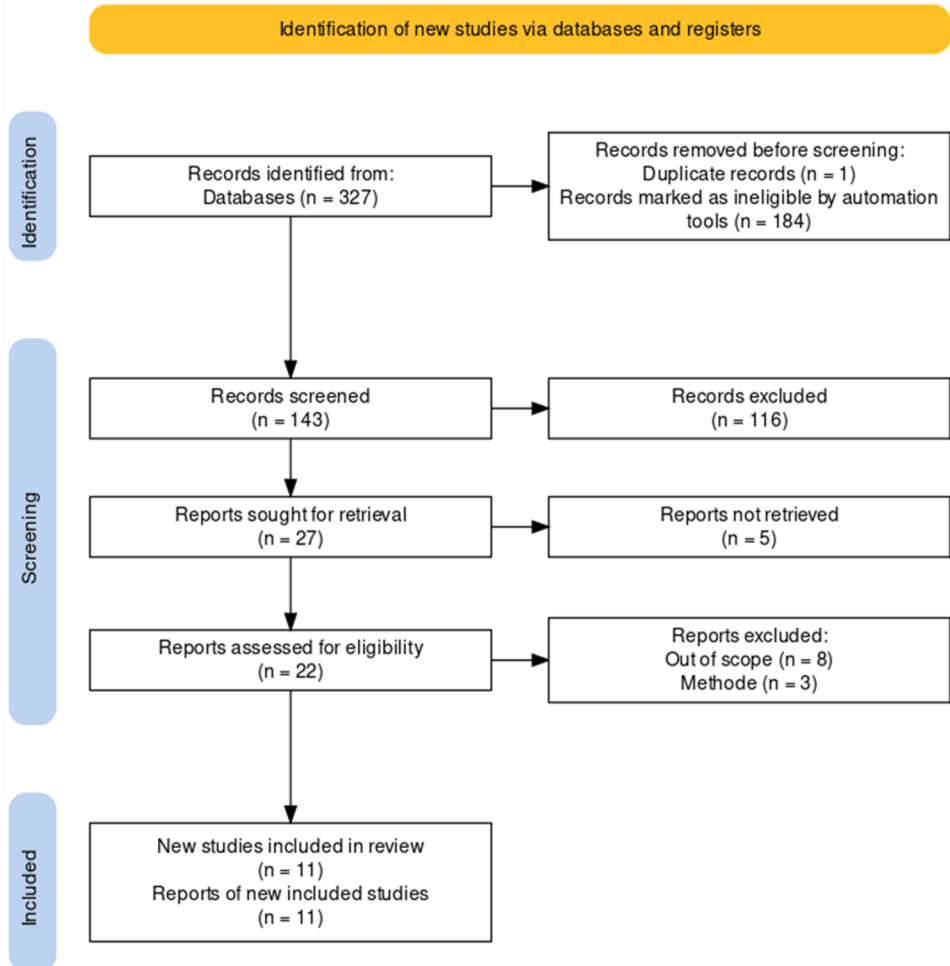


Fig.1. Flow diagram of search strategy and article selection

A summary of each intervention and effect demonstrated effect of inhibition ACE can be found in Table 1.

Table 1. Summary of Evidence

Author	Models	Type Study, induced	Effect Observed
Salama, et al. [7]	Myocardial Infarction	Experimental In Vivo Epinephrine 100 mg/kg	The ginseng extract reduces infarct size through its cardio- and reno-protective properties, maintains heart and kidney function by activating Nrf2 and downregulating NF-κB, PKC, AT ₁ R and iNOS
Li, et al. [8]	Diabetes	Experimental In Vivo	Protective effect of the AT ₂ R agonist B-Pro7 Ang III in models of hypertension and

		Streptozotocin 55 mg/kg in 0,1 M citric acid	diabetes accompanied by fibrosis. When RAS inhibition is contraindicated, stimulation of AT ₂ R with an Ang III is an added therapeutic option for hypertension and diabetes treatment.
Sánchez-Aguilar M, et al. [9]	Metabolic Syndrome (MetS)	Experimental In Vivo 30% sugar solution	Fenofibrate has been able activate PPAR-alpha which can prevents damage due to ischemia. Angiotensin (1-7) / AT ₂ axis and inhibits the Angiotensin III/Angiotensin IV signalling pathway.
Sukumaran, et al. [10]	Heart failure	Experimental In Vivo Immunization (The porcine cardiac myosin was dissolved in phosphate-buffered saline at 5 mg/ml and emulsified with an equal volume of Freund's adjuvant containing 11 mg/ml Mycobacterium tuberculosis H37RA 5mg/ml)	Myocardial MAPK pathways are activated in experimental autoimmune myocarditis (EAM) rats, and olmesartan therapy decreases p38MAPK and JNK activation, suggesting that Ang II mediates stress signaling-mediated MAPK signaling.
Nguyen ITN, et al. [11]	Heart disease	Experimental In Vivo N-ω-nitro-L-arginine (L-NNA) (40mg/kg/day)	Sodium Thiosulfate or Lisinopril can be mediated via common pathway associated with oxidative stress in angiotensin II.
Salem MA, et al. [12]	Hypertension	Experimental In Vivo N-ω-Nitro-L-Arginine methylester (L-NAME) (40mg/kg)	The vasodilation via eNOS/iNOS/NO pathway
Silva, et al. [13]	Combining Hypertension and Diabetes	Experimental in vivo Streptozotocin 50mg/kg in sodium citrate buffer pH 4.5	AT ₁ pathway inhibition provides neuroprotection for diabetic retinopathy by improving antioxidant and mitochondrial function.
Regenhardt RW, et al. [14]	Ischaemic stroke	Experimental In Vivo Middle cerebral artery occlusion (MCAO)	Reduced nitric oxide secretion, and decreased level of IL-1 beta, IL6 and CD11B. antiinflammatory action of Ang-(1-7) in the brain, and cerebroprotective.
Mecca AP, et al. [15]	Ischaemic stroke	Experimental In Vivo	Reduction of cerebral infarction volume. Ang-(1-7)-MasR can be cerebroprotective

		Middle cerebral artery occlusion (MCAO)	during ischaemic stroke includes blunting of inducible nitric oxide synthase expression
Durand MJ, et al. [16]	Endothelial dysfunction	Experimental In Vivo High salt	Cellular mechanism by which chronic Ang-(1-7) treatment lowers vascular superoxide levels and preserves NO
Ola, et al. [17]	Diabetic	Experimental In Vivo Streptozotocin 55mg/kg in 100 mM sodium citrate buffer, pH 4.5	By inhibiting AT ₁ R, Telmisartan (10mg/kg/day) increases brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF) and tyrosine hydroxylase (TH) levels in diabetic retinas
Regenhardt RW, et al. [18]	Hemorrhagic stroke	Experimental In Vivo Stroke-in spontaneously hypertension (spSHR)	Decreased microglial activation and improved neurological function

Angiotensin Converting Enzyme (ACE) is a dipeptidyl carboxypeptidase with a zinc atom. The highest concentration of ACE is found in pulmonary capillaries. ACE is also present in the proximal tubules of the kidney gastrointestinal tract, cardiac organs, and brain. ACE appears as a membrane-bound enzyme as well as a globular circulatory enzyme [19]. ACE and AT₁R inhibition increases basal NO release and coronary or arm blood flow responses to acetylcholine [20]. The mechanism begins with the emergence of risk factors such as age, family history, metabolic syndrome, diabetes mellitus, dyslipidaemia, obesity, smoking, and stress that lead to increased vascular resistance, resulting in decreased blood flow to the kidneys, which causes to stimulate the release of renin enzyme stored in the renal juxtaglomerular cells to convert angiotensinogen (renin substrate) into angiotensinogen I (inactive decapeptide) [21]. Angiotensin I is then converted by ACE, a dipeptidyl carboxypeptidase that splits histidyl-leucine from inactive angiotensin I into angiotensin II. Angiotensin II causes arteriolar vasoconstriction, resulting in increased peripheral resistance and blood pressure. In addition, angiotensin II can also stimulate the adrenal cortex, thereby triggering the release of aldosterone, triggering an increase in sodium ion reabsorption in the kidneys and triggering an increase in water reabsorption increasing blood pressure [22].

Besides catalysing the formation of angiotensin II, ACE also catalyses the degradation of bradykinin. In contrast to angiotensin II, bradykinin exerts vasodilatory, anti-inflammatory, ROS-lowering and antifibrinolytic, and antithrombotic effects [23]. The benefits of bradykinin are mediated by bradykinin-induced release of nitric oxide (NO). NO is a vasodilating factor in tissues, the main regulator of endothelium function [24].

The production of NO from endothelial cells is promoted by eNOS with stimulation from acetylcholine and shear stress via receptor and nonreceptor, calcium-dependent and calcium-independent pathways [25]. In the presence of endothelial cell dysfunction, the influence of acetylcholine on vascular smooth muscle cells directly causes constriction and inhibits the release of NO into the lumen. Vasoconstriction increases shear stress, the most potent physiological stimulation for NO production [26]. The imbalance of angiotensin II and bradykinin with increased levels of angiotensin II and reduced levels of bradykinin due to ACE overexpression ultimately leads to endothelial dysfunction. By targeting ACE, ACE

drugs not only inhibit the formation of angiotensin II alone, but also act to increase the availability and prevent the degradation of bradykinin [27].

Mechanism of ACEI Effect as Cardioprotective in Cardiovascular Events

ACEIs can reduce the level of angiotensin II in the blood circulation, which promotes vasodilation and reduces systemic vascular resistance. Reduced angiotensin II also reduces the formation of aldosterone, thereby reducing sodium resistance [28]. Effects on the endothelium where the endothelium has an important role in maintaining the condition of blood vessels. The endothelium functions in the regulation of vascular tone, coagulation, cell growth and death, and leucocyte migration. Endothelial function is influenced by the balance between vasodilators (such as NO) and vasoconstrictors (such as angiotensin II). Increased levels of angiotensin II in the endothelium will stimulate NADH and NADPH oxidase which causes the formation of Reactive Oxygen Species (ROS), resulting in oxidative stress conditions in the endothelium. This condition causes endothelial cell dysfunction, cell growth and triggers inflammation which can result in vascular inflammation and thrombosis [29]. ACEI can reduce the production of angiotensin II so that endothelial function can be maintained [27].

Angiotensin II stimulates matrix metalloproteinase (MMP) enzymes in atherogenesis. MMPs can damage the extracellular matrix in plaques, thus affecting plaque stability and disruption. ACEIs can minimise the inhibition of angiotensin II formation [30]. Effects on cardiac ischaemia where during myocardial ischaemia, the sympathetic nervous system is activated with an increase in norepinephrine and epinephrine. Increased levels of these circulating neurohormones will cause systemic vasoconstriction [31]. On the other hand, blood pressure is one of the main determinants of myocardial oxygen demand. When blood pressure increases, left ventricular afterload will also increase. ACEI have been shown to limit the activation of these neurohormones and vasoconstriction during ischaemia [32].

ACE plays a role in reducing remodelling and lowering the mortality rate of post-myocardial infarction patients. Remodelling is essentially a protective mechanism. However, remodelling then leads to inappropriate cardiac hypertrophy and reduced cardiac function. This eventually results in heart failure and death [33]. A hyperactive RAAS may result in protection against cardiac remodelling. Overexpression of angiotensin II-converting enzyme can prevent cardiac remodelling due to the formation of Ang (1-7). Angiotensin II through its interaction with AT₁R increases fibroblast gene expression (including collagen), fibroblast density and proliferation and myocyte hypertrophy, all of which are hallmarks of myocardial fibrosis and cardiac remodelling [34]. Decreased expression of ACE2 results in an imbalance in RAAS to AT₁R resulting in disease progression. Increasing ACE2 (through gene therapy, rhACE2 or ACE2 activators) can restore the balance of the renin angiotensin system to Ang 1-7/Mas receptors which has the potential to protect against disease [35].

A cardiac remodeling known as myocardial infarction (MI) results from maladaptation at the molecular, cellular, tissue, and organ levels to cardiac stress and the creation of oxygen-derived free radicals in the heart, which causes cardiomyocyte necrosis and apoptosis [36]. Renal complications are a core component of MI caused by intraperitoneal injection of adrenaline. Rats with MI caused by catecholamines (epinephrine, nor epinephrine and isoproterenol) serve as models for examining the effects of different cardioprotective medications, and these models closely resemble human MI [7]. Epinephrine injection significantly increased cardiac NO content as compared to the normal control group, which may indicate its function in epinephrine-induced MI. Nrf2, a crucial antioxidant regulator of cardiovascular homeostasis, suppresses oxidative stress, which is linked to rat heart damage, and its target genes [37]. In the heart and kidney, ginseng extract inhibited protein kinase C (PKC) activity and AT₁R indicating that it prevented membrane-bound NAD(P)H oxidase, hence reducing mitochondrial dysfunction and apoptosis [7]. High amounts of saponins found ginseng, such as ginsenosides, reduce inflammation and oxidative stress, with slows the course of kidney impairment in type 1 diabetes [38].

Dendritic cells (DC) play a key role in the development of myocardial infarction (MI). Angiotensin-converting enzyme (ACE) activity can be influenced by ACE inhibitor therapy in MI mice. According to the present study, ACEI significantly reduced mobilization of DCs from the spleen, lowered their numbers in the peripheral circulation and infarct region in mice models via AT₂R. Moreover, ACEI repressed DCs maturation and inflammatory response by regulating AT₂R expression. Thus, the role of AT₂R in the process of DCs regulation by ACEI could provide new therapeutic strategies [39]. AT₂R activation counteracts AT₁R-mediated actions, which are believed to be beneficial for the heart in most cases [40].

Metabolic syndrome in rats induced by 30% sugar solution shows symptoms of hypertension, dyslipidemia (high triglyceride levels), hyperinsulinemia and insulin resistance. In rats with metabolic syndrome showed high serum CK activity [9]. In both human and animal models, serum CK activity is recognized as a biomarker of cardiac risk, however this parameter is unspecific [41]. Treatment with fenofibrate reverses some of the effects caused by these pathologies by regulating Ang II/AT1-mediated processes such as energy metabolism, oxidative stress, inflammation, and cell differentiation [43]. The elevated production of ACE2 during ischemia implies that this enzyme has a protective function [44]. Increasing evidence suggests, however, that RAS can be triggered in an alternative pathway, such as Ang-(1-7) and its cardioprotective effects [9].

Cardiac fibrosis has been seen to rise when diabetes is induced with streptozotocin (STZ) in spontaneously-hypertensive rats (SHR) [8]. Increased aortic fibrosis with diabetes. Diabetes was associated with greater aortic fibrosis in the current study. On the other hand, β -Pro7Ang III decreased the levels of vascular MCP-1, CD68, and DHE, suggesting a strong anti-inflammatory and antioxidant effect. These findings are fully in line with the vascular alterations brought about by C21 in stroke-prone SHR and diabetic ApoE^{-/-}-mice, where endothelial function was also restored [42].

Dilated cardiomyopathy is the result of the recurrent form of experimental autoimmune myocarditis (EAM), which is modeled after human giant cell myocarditis in rats. T cell activation causes EAM, with the heart exhibiting the highest level of inflammation around day 21 following vaccination [43]. According to some data, cellular immune pathways may play a part in the pathophysiology of myocarditis[10]. Ang-II induced ROS activation in remodeling left ventricular (LV) myocardium of EAM rats. The myocardial expressions of growth arrest and DNA damage-inducible gene, caspase-12, phosphor-p38 mitogen-activated protein kinase (MAPK), phospho-JNK, and glucose-regulated protein-78 were all down-regulated in response to olmesartan treatment [10]. ROS produced by NADPH oxidase activation is aessential for heart and vascular remodeling, fibrosis, and hypertrophy [44]. NADPH oxidase activation has also been observed in animals (mice) with pressure overload-induced LV hypertrophy[45].

Orally given Sodium Thiosulfate (STS) reduces hypertension, left ventricular hypertrophy, fibrosis, and systemic oxidative stress to the same degree as ACE inhibition while also improving systolic function. These results suggest that oral STS therapy has significant cardioprotective qualities and may be therapeutic for hypertensive heart disease [11]. In smooth muscle cells, STS may react through a variety of thiol processes involving transsulfuration enzymes with cysteine to create H₂S [46]. By blocking intracardiac angiotensin II activity, H₂S significantly inhibited the development of cardiac fibrosis and reduced the amount of collagen in the cardiac tissue [47]. That using STS orally lowers systemic oxidative stress, as shown by a decreased excretion of thiobarbituric acid reactive substances (TBARS) assay. With its vasodilator qualities, STS's antioxidant actions might also have a role in cardioprotection [11].

Mechanism of ACEI Effect as Neuroprotective in Cerebrovascular Events.

RAAS is a key regulator of blood pressure and electrolyte homeostasis. In addition to its importance as a regulator of cardiovascular function, the RAAS is also associated with the modulation of brain function, including cognition, memory, sensory, depression, and anxiety [48]. The RAAS cascade is initiated by the renin secretion from juxtaglomerular cells into the circulation, which triggers the production of angiotensin II [49]. Angiotensin II affects the cerebral circulation through its receptors, namely AT₁, AT₂ and AT₄ [50]. Angiotensin II Type 1 receptor (AT₁R) is responsible for the physiological effects of RAAS. Overstimulation of AT₁R can cause disease [51], such as affecting infarct volume growth [50]. Overactive RAAS can be controlled by reducing angiotensin II through the renin pathway with ACE inhibitors or by blocking AT₁R with angiotensin receptor blockers (ARBs) [51].

Angiotensin II receptor inhibition has shown various neuroprotective effects through central and peripheral actions [50]. Activation of AT₂ receptors post-stroke can stimulate nerve growth and promote nerve repair under hypoxic conditions [52]. AT₁ receptor blockage was shown to play a role in neuroprotection during hypoxia through decreased oxidative stress. Increased angiotensin levels during AT₁ receptor inhibition will affect the degradation rate of angiotensin I and angiotensin II, resulting in biological functions through different receptor subtypes. This peptide contains angiotensin fragments 1-7, 2-8 (angiotensin 3) and 3-8 (angiotensin 4) that act on AT₁(1-7) and AT₄ receptors. Activation of Ang(1-7) decreases oxidative stress and minimizes neuronal death by reducing nitric oxide secretion and inhibiting NF- κ B and TNF- α [53]. NF- κ B inhibition was shown to prevent the increase in vascular adhesion protein-1 by angiotensin II and a reduction in leukocyte chemotaxis and adhesion [54]. Another neuroprotective mechanism of angiotensin II receptor inhibition is the maintenance of blood-brain barrier integrity by protecting against the effects of hypertension and diabetes mellitus and preventing macrophage infiltration [50]. The neuroprotective effect of angiotensin receptor inhibition is related to a decrease in AT₁ receptor activation or the occurrence of AT₂ receptor activation. Stimulation of AT₂ receptors triggers nerve regeneration and has a neurotrophic role [55]. These properties of ACE inhibition and angiotensin II receptor inhibition are directly related to the effects of angiotensin II on AT₁, AT₂, and Mas receptors [50].

Tumour Necrosis factor- α (TNF- α) is a proinflammatory cytokine whose production is stimulated by angiotensin II and which is associated with interstitial fibrosis through myofibroblast differentiation and NF- κ B activation. TNF- α has proinflammatory and immunoregulatory functions. TNF- α produces various biological effects, including cellular differentiation, proliferation, and apoptosis [56]. The transcription factor NF- κ B regulates the induction and resolution of inflammation. In addition, NF- κ B regulates the expression of many genes that play key roles in the inflammatory response [57].

Angiotensin II affects cerebral blood flow via the AT₁, AT₂, and AT₄ receptors. Angiotensin II primarily affects AT₁ receptors by cerebral vasoconstriction, pro-inflammatory effects, and enhanced reactive oxygen species production. These all result in hypertension and cerebral circulation disturbance, which open the door for cerebral ischemia and cellular death. Activation of the AT₁ receptor will impact the expansion of the infarction volume and entail the injury of the penumbra [58,59]. Angiotensin II receptor blockers' central effect has the benefit of not requiring blood-brain barrier passage. Direct control over cerebral circulation can be obtained by inhibiting AT₁ receptors in the cerebrovascular endothelium of the major arteries and cerebral microcirculation. AT₂ receptor activation promotes neuronal development and improves survival in low-oxygen environments following a stroke. It has been demonstrated that blocking AT₁ receptors contributes to neuronal protection during hypoxia by reducing oxidative stress [60].

ACE inhibitors and angiotensin receptor blockers have distinct pharmacodynamic effects on AT₂ receptors. ACE medications increase AT₁ and AT₂ receptors while decreasing the production of angiotensin II. Angiotensin II production is increased when AT₁ receptors are

inhibited, and AT₂ receptors are stimulated by renin release and inhibition of negative feedback. Angiotensin II receptor blocker selectively inhibited AT₁ receptors, enabling angiotensin II to stimulate AT₂ and AT₄ receptors. As a result, this medication family appears to have a stroke-prevention benefit separate from its antihypertensive benefit. Several meta-analysis studies also support the same notion. Additionally, the same studies demonstrate that angiotensin II receptor blockers, as opposed to ACE inhibitors and beta-blockers, lower the synthesis of angiotensin II and have a more substantial neuroprotective impact [61].

As a neuronal tissue, the retina expresses neurotrophic factors that are essential for cell survival. Researchers have reported reduced levels of neurotrophins, mainly brain-derived neurotrophic factor (BDNF), in diabetic retina [62]. Diabetes also causes oxidative stress and neurodegeneration due to reduced levels of BDNF. In oxidative stress-induced neurogenic hypertension, BDNF participates in maintaining oxidative stress. The benefits of AT₁R blockers, such as telmisartan, in reducing oxidative stress and inflammation in the retinal microvasculature have been thoroughly investigated. BDNF is one of the neurotrophins that is thought to be neuroprotective in situations of metabolic stress, including diabetes [63].

4 Conclusion

That RAS can be triggered in an alternative pathway, such as Ang-(1-7) and its cardioprotective effects. AT₂R activation counteracts AT₁R-mediated actions, which are believed to be beneficial for the cardiac. The neuroprotective effect of angiotensin receptor inhibition is related to a decrease in AT₁ receptor activation or the occurrence of AT₂ receptor activation. ACE inhibition and angiotensin II receptor inhibition are directly related to the effects of angiotensin II on AT₁, AT₂, and Mas receptors.

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