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Neuroprotective Effect Of Angiotensin Receptor Blocker

Syarinta Adenina[1*], Nita Parisa[1], Rulan Adnindya[2]

[1]Departement of Pharmacology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2]Departement of Anatomy, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

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Corresponding author:
Syarinta Adenina
E-mail address:
masayusyarintaadenina@fk.unsri.ac.id

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ABSTRACT

Angiotensin Receptor Blocker, ARB, is a drug that acts on the AT1 receptor so as to inhibit Ang II stimulation. Ang II stimulates the main activity of the angiotensin renin system. Recent research has shown the presence of components of the RAS system in the brain, and the neuroprotective effects of the brain. ARB drugs can enter the brain and protect the blood brain flow, maintain the function of the blood brain barrier and reduce cerebral hemorrhage. The neuroprotective effect of ARB not only arises from improved cerebrovascular blood flow (improved access to oxygen and nutrients) but also decreased factors that can cause brain injury, including decreased excitotoxicity of glutamate which causes inflammatory response and apoptosis, decreased inflammatory response of interleukin-1β and bacterial endotoxin. In addition, there are additional effects through the PPARγ activation mechanism. Based on these benefits ARBs can be developed for the purpose of treating various brain disorders, in this case improving cognitive function, such as vascular dementia, Alzheimer's disease, Parkinson's disease, traumatic brain injury, stroke, and others.

1. Introduction

The renin-angiotensin system (RAS) is well-known as a humoral circulatory system involved in blood pressure regulation and homeostasis. This system is expressed in many organs, including the brain. RAS activation is a result of angiotensin II stimulation at angiotensin II type I (AT1R) receptors. Uncontrolled stimulation of AT1R is associated with the development and progression of various pathological processes, including vascular and tissue inflammation, increased insulin resistance, and failure to regulate blood flow. AT1R has an extremely high expression in cerebrovascular endothelial cells. In the brain, increased activation of AT1 receptors associated with cerebrovascular dysfunction causes hypoxia, decreased nutrient intake and metabolic changes, oxidative stress, inflammation, and changes in blood-brain barrier function. This process causes cell damage and decreases cognition function. In addition to AT1 receptors, RAS also has other receptors that work opposite to AT1R, namely AT2 receptors and Mas receptors. These two receptors mediate various protective and tissue-regenerating actions, including anti-inflammatory, antifibrotic or neuro-regenerative effects, vasodilation and other beneficial metabolic actions. [1,2]

Angiotensin II receptor blockers (ARBs) are widely known to be effective in the treatment of cardiovascular disease, kidney, metabolic syndrome, and diabetes. Recent research suggests ARB's neuroprotective effects, making them potential for the treatment of brain disorders. Several clinical trials report antihypertensive drugs that modulate RAS such as ARBs or ACE inhibitors are associated with decreased incidence of Alzheimer's disease and decreased cognitive function in patients with mild cognitive impairment. ARBs can improve inflammatory responses and apoptosis to glutamate, interleukin 1β, and bacterial endotoxins in cultures of neurons, astrocytes, microglial and endothelial cerebrovascular cells. In animal studies with experimental stroke, brain trauma, Alzheimer's, and Parkinson's disease, ARBs have known can enter the brain, protect brain blood flow, maintain blood-brain barrier function, and reduce brain hemorrhage, brain inflammation and neuron damage.[1,3]

These ARBs may decrease the expression of lipopolysaccharide receptors (LPS) and IL-1β, and decrease the stimulation of NMDA glutamate receptors. In adipose tissue, ARBs could increase

adiponectin levels, which are neuroprotective, and improve insulin and hyperinsulinemia in patients with essential hypertension. Insulin can cross the blood-brain barrier and compete with Aβ for insulin-degrading enzymes in the brain. This leads to decreased degradation and accumulation of Aβ.[1]

These various neuroprotective effects of ARBs may be a new hope for the treatment of brain disorders, such as Alzheimer's disease. To understand more about ARBs and their neuroprotective effects, this paper will discuss the angiotensin renin system, drugs belonging to the ARB class both pharmacokinetics and neuroprotective effects caused by these drugs.

2. Renin-Angiotensin System (RAS)

The Renin Angiotensin System (RAS) plays a role in blood pressure regulation and electrolyte-body fluid homeostasis. Activation of this system is preceded by prorenin, which is secreted in response to increased sympathetic nerve activity or decreased blood pressure, extracellular fluid volume, and extracellular sodium concentration levels. Prorenin is converted to renin. Renin is synthesized, stored, and secreted into the renal arterial circulation by granular juxtaglomerular cells. Renin is the main determinant of the rate of angiotensin II production. Renin will break the bond between residues 10 and 11 at the end of the angiotensinogen amino acid to produce angiotensin I, which is converted later into Angiotensin II with the help of Angiotensin-converting enzyme (ACE). When renin secretion increases, the formation of angiotensin II will also increase, and angiotensin II will stimulate AT1 receptors to inhibit renin release.[4–6]

There are two subtypes of angiotensin receptors called AT1 and AT2 receptors. The AT1 receptor activates large signal transduction systems, including calcium intake and release, phospholipases, mitogen-activated protein kinase, janus kinase, protein kinases (serine/threonine), nonreceptor tyrosine kinases, small proteins that bind to GTP, transcription factors, factors affecting translational efficiency, and pathways resulting in the production of reactive oxygen species. Stimulation of Ang II receptors activates phospholipase C (PLC). This PLC is a membrane-bonded enzyme that hydrolyzes phosphatidylinositol-4,5-bisphosphate (IP2) to produce inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 causes calcium mobilization from the endoplasmic reticulum, resulting in increased calcium in the cytoplasm. As a result, there is depolarization of cell membranes and the opening of calcium channels. Calcium will enter the cells and cause vascular smooth muscle cell contraction (vasoconstriction). AT1 receptors also stimulate membrane-bound NADP/NADPH oxidase that produces superoxide anions. AT1 receptors are widely expressed in cerebrovascular endothelial cells, these brain endothelial cells form basic anastomosis of the blood-brain barrier that prevents the uncontrolled entry of ions, amino acids, and peptides into the brain. AT1 receptors are also expressed on selective neuronal circuits and in astrocytes. The action of Ang II on AT1 receptors causes vasoconstriction, renal tubular natrium reabsorption, aldosterone and vasopressin release, vascular smooth muscle changes, and stimulation of central and peripheral sympathetic work that leads to an increase in blood volume and blood pressure. In addition, Ang II through the signaling pathway in AT1 can also lead to brain ischemia and inflammation, as well as changes in mood and memory. [1,5–9]

AT2 receptors are widely expressed in fetal tissue, the uterus, adrenal medular tissue, and the brain (in the cerebrovascular wall, and in the thalamus, hypothalamus, brainstem, and other locations). Until this day, AT2 signaling pathway is still a puzzle. But in vitro tests show that activation of the AT2 receptor is thought to cause activation of tropomyosin-related kinase receptor A (Trk A) and its effector p42/p44 mitogen-activated protein kinase (ERKs) 1 and 2, the release of nitrite oxide (NO) and activation of protein kinase B (Akt). In animals, AT2 activation decreases the area of infarction after ischemic injury by increasing cerebral perfusion in the penumbra, decreasing superoxide production, activating neuron system repair by supporting neuronal cell differentiation and neurite growth, and decreasing inflammation and axon degeneration. These AT2 receptors play a role in mediating the protective effects of Ang II such as vasodilation, anti-inflammation and inhibition of vasopressin secretion. AT1 and AT2 receptors have opposite effects on blood pressure which is thought to be because AT1 and AT2 receptors are generally located on different neurons so each receptor can separately affect the neuronal circuits that control blood pressure. These AT2 receptors are upregulated in pathophysiological processes such as cardiac remodeling followed by hypertension and myocardial infarction, heart failure and stroke. Currently, there are two types of drugs that can completely block RAS, namely renin inhibitors and angiotensin II receptor antagonists. [3,4,8,10,11]

3. Neuroprotective Effect of Angiotensin Receptor Blocker (ARB)

Overstimulation of AT1 receptors can lead to inflammation and apoptotic signaling activity. AngII-induced toxicity mechanisms include increased nicotinamide adenine dinucleotide phosphate oxidase (NADPH) activity leading to the formation of intracellular reactive oxygen species (ROS). Then, increased production of reactive oxygen species activates sensitive-redox recognition molecules, such as mitogen-activated protein kinases, e.g. p38 mitogen-activated protein kinase, NH-2 terminal kinase (JNK), and extracellular signals regulated kinase 1 and 2. The formation of ROS can accelerate

the inflammatory process and apoptosis. Mitochondria play an important role in the induction of apoptosis after oxidative stress. Both in vitro and in vivo studies suggest mitochondrial energy metabolism is overly sensitive to ROS destruction, and excess ROS synthesis leads to mitochondrial swelling followed by cell damage.[1,9]

Other inflammatory mechanisms can occur through activation of cyclooxygenase-2 due to prostaglandin production, increased levels of nitrite oxide (NO) and stimulation of extracellular signaling pathways – regulated by kinases 1 and 2/protein kinase c/ diacylglycerol (DAG). Activation of this pathway leads to an increase in intranuclear transcription factors such as nuclear factor-kappa B with increased production of proinflammatory neurotoxic cytokines such as IL-1β, TNFα, IL-6, and monocyte chemotactic protein 1 (MCP-1) This activation of NF-κB can also downregulate peroxisome proliferator-activated receptors (PPARs). PPARs are anti-inflammatory. Resulting in a significant inflammatory response and increased apoptosis. [1]

ARBs can inhibit the effects caused by Ang II so that there is a decrease in inflammation in the brain parenchyma. ARBs can cross the blood-brain barrier and penetrate depending on the lipophilic nature of each ARB/compound. Telmisartan, which has the highest lipophilic properties of other ARB drugs, is reported to penetrate directly into the brain and reach relevant therapeutic concentrations after systemic administration. In chronic administration or in pathological conditions where the blood-brain barrier is damaged, ARB concentrations may increase. [1]

In addition to its direct effect on AT1 receptors, ARBs also protect the brain from various damage factors through complex interactions between membrane receptors and their signal transduction. ARBs may provide protection against bacterial endotoxins. LPS is the main toxin typical of gram-negative bacteria. The presence of LPS will induce inflammation and apoptosis. In primary neuron cultures, LPS has been shown to increase AT1 receptor expression, while ARBs downregulate CD14 transcription, thereby decreasing the effect of LPS at receptor levels. ARBs decrease the transduction mechanism of proinflammatory signals due to the stimulation of AT1 and CD14/TLR4 receptors. This anti-inflammatory effect exerts a neuroprotective effect against LPS-induced injury. [1,7,12]

ARBs directly protect neuron cultures from the inflammatory and proapoptotic effects of overstimulation of IL-1β. In primary cortical neurons, ARBs decrease cyclooxygenase-2 expression and prostaglandin E2 productions which are induced by IL-1β. [1]

ARBs also have a neuroprotective effect against glutamate toxicity. ARB administration decreases neuron injury caused by stimulation of N-methyl-D-aspartate receptors from neurotoxic glutamate levels. The mechanism is by decreasing N-methyl-D-aspartate receptor expression, decreasing activation of caspase 3 proapoptosis, protecting of the phosphoinositide-3-kinase/protein kinase B/Akt/glycogen synthase kinase 3 beta defense pathway, and decreasing in neurotoxic inflammation. In addition, excessive activation of N-methyl-d-aspartate receptors activates transcriptional upregulation and expression of AT1 receptors, thereby increasing the proapoptotic and proinflammatory activity of AT1 receptors. [1]

Some ARBs emit beneficial effects that are not directly related to AT1 receptor inhibition. This was seen in cell cultures that had low Ang II, in cells that did not express AT1 receptors such as circulating monocytes and rodent microglia, and in knockout AT1 receptors mice. This is thought to be through the role of ARB on PPAR gamma. [1]

Telmisartan, candesartan and losartan can activate PPAR gamma (PPARγ). PPARγ activation is beneficial on carbohydrate and lipid metabolism and directly protects vascularity. Other beneficial effect of ARBs is vascular protection and insulin sensitivity and glucose metabolism improvement. The result of AT1 receptor inhibition and PPARγ activation is the energy balance and improved blood flow to the brain. Activation of PPARγ has been shown can decrease inflammation and protect cognition. [1]

AngII can bind to Ang II type II (AT2) receptors. Stimulation of AT2 receptors is thought to compensate for AT1 receptor activity. Inhibition of AT1 receptor causes Ang II production to increase which results in increased activation of AT2 receptors and multiplication of neuroprotection mechanisms. However, the role of AT2 receptors has not yet been clarified. Umschweif et al. found that activation of AT2 receptors is beneficial in improving cognitive and motor function, and decreasing the volume of brain lesions after traumatic brain injury. AT2 receptors improve cognitive function allegedly through improved microcirculation and cerebral blood flow as a result of the presence of bradykinin and the production of NO. NO production resulting in cerebrovascular relaxation and improved blood flow after injury. [1,10]

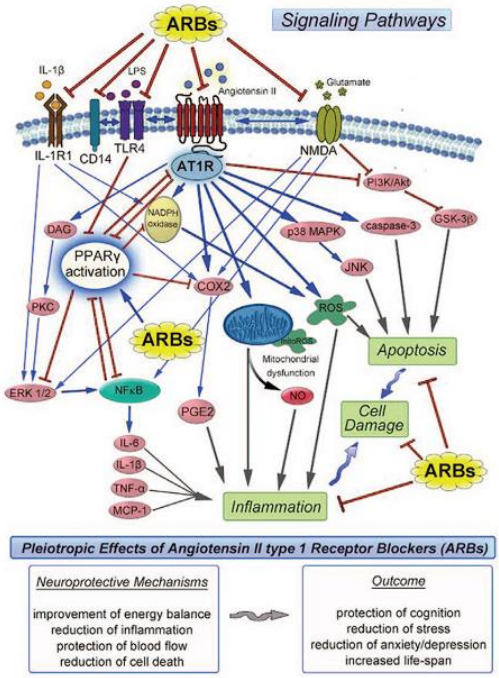

Figure 1 ARB Signal Line[1]

Inflammatory signals and apoptosis occur due to overstimulation of AT1 receptors and interaction between AT1 receptors and other banned receptors (interleukin 1 beta, lipopolysaccharides, glutamate), which can eventually aggravate cell damage. NADP activation and increased ROS lead to mitochondrial dysfunction with the abundant mitochondrial formation of ROS, which adds to inflammatory and apoptosis signals. Other inflammatory mechanisms are the formation of COX-2 with the production of inflammatory prostaglandins, increased levels of toxic nitrite oxide and stimulation of the DAG/PKC/ERK 1/2 pathway which increases intranuclear transcription factors such as nuclear factor-kappa B. NF-kB increases the production of proinflammatory neurotoxic cytokines such as IL-1β, TNF-α, IL-6, MCP-1. While proapoptotic signaling occurs through a decrease in the PI-3K / PKB / Akt / Glycogen synthase kinase 3 β defense pathway, activation of caspase-3, and stimulation of protein kinase activated by mitogen p38 and JNK. In addition, overstimulation of AT1 receptors can inhibit PPARγ. LPS : Lipopolisakarida, ROS : Reactive Oxygen Species, NADP : Nicotinamide adenine dinucleotide phosphate, DAG : Diacylglycerol, PKC : Protein kinase C, ERK ½ : extracellular signal-regulated kinase 1 and 2 pathway, MCP 1 : Monocyte chemotactic protein 1 , PI-3K : phosphoinositide-3-kinase, JNK : c-Jun-N Terminal Kinase, PPARγ : peroxisome proliferator activated receptor gamma, NMDA : N-methyl-d-aspartate, GSK3β : glycogen synthase kinase 3 β

In addition, ARBs can also cause neuroprotective effects by maintaining the integrity of the blood-brain barrier. Blood-brain barrier damage plays a role in macrophage infiltration and the passage of injury factors in the circulation to the brain parenchyma. AT1 receptors, in addition to being widely expressed in endothelial cells of the brain, also have high concentrations in circumventricular organs outside the blood-brain barrier. Injury to the cerebrovascular endothelium causes damage to the blood-brain barrier, cell infiltration into the brain parenchyma and increased inflammation and oxidative damage. This leads to a decrease in the supply of oxygen and nutrients to the brain, which when left unchecked can lead to progressive cellular injury and death. In cerebrovascular endothelial cells and vascular smooth muscle cells of large arteries and cerebral microvascular, ARBs block AT1 receptors thus countering increased vasoconstriction and vascular hypertrophy and Ang-II-driven remodeling. This leads to decreased brain ischemia, susceptibility to stroke, or continued cell death of traumatic brain injury. [1,9,13]

ARBs regulate hormone production and release in the anterior pituitary cell parenchyma that regulates reproductive hormones and reactions to stress. In the adrenal zona glomerulus, AT1 receptors regulate the production and release of aldosterone, a major proinflammatory factor in the brain and peripherally. ARBs play a role in the regulation of responses to stress through peripheral sympathetic nerve activity, vagal activity and transport, and regulation of pain perception. Both the terminal sympathetic nerves that regulate norepinephrine release, peripheral sympathetic activity, blood flow and the vagal motor nucleus express a number of AT1 receptors. So, ARBs can prevent inflammatory signals transfers being passed on to the brain. [1]

By decreasing various pathogenic factors in the brain, leading to persistent neuron and axon injury, ARBs can improve the development and course of various brain diseases, improve outcomes and decrease disability. These pathogenic phenomena such as excess oxidative stress, changes in cerebral blood flow such as ischemia and dysregulation of brain autoregulation, mitochondrial dysfunction, neurotoxic inflammation and accumulation of amyloid-β proteins associated with traumatic brain

injury, spinal cord injury, stroke, Alzheimer's and Parkinson's disease and mood disorders. In studies with cortical injured rodents, ARBs have been shown to decrease volume lesion, inflammation and protect motoric and cognitive performance. [1]

ARBs lower all major risk factors for Alzheimer's disease, such as regulating blood pressure, limiting stroke damage and improving diabetes. ARB drugs can increase adiponectin levels and improve insulin resistance, where hyperinsulinemia is often associated with cognitive impairment in diabetic patients. Chronic hyperinsulinemia may provide a competitive substrate against enzymes that degrade insulin, thereby decreasing the degradation and accumulation of amyloid-β. Amyloid-β accumulation is regulated by a balance of production and clearance through proteolysis or transport across the blood-brain barrier. Proteolytic degradation is aided by insulin degradation enzymes, ACE or neprilisin (NEP). Insulin can cross the blood-brain barrier into the central nervous system and compete with amyloid-β for enzymes that degrade insulin in the brain, especially the hippocampus. While in the periphery, hyperinsulinemia can inhibit insulin production in the brain resulting in amyloid clearance disorders and an increased risk of Alzheimer's disease. In rodents with Parkinon's disease, stimulation of AT1 receptors increases inflammation and injures dopaminergic cells. Administration of ARBs improves dopaminergic cell death, decreases motor deficiency, protects rodents from neurotoxins. [1,9,11,13]

4. Angiotensin Receptor Blocker (ARB)

ARB drugs are derivatives of imidazole that have an effect on Ang II inhibitory and highly selective against AT1 receptors. This drug can increase the activity of Ang II at the AT2 receptor and affect the conversion of Ang II to other RAS mediators such as Ang (1-7) by ACE2 acting on the MAS receptor. There are eight ARBs available in the market for the treatment of hypertension namely telmisartan, olmesartan, candesartan, losartan, valsartan, irbesartan, azilsartan, and eprosartan. Some ARBs that can penetrate the blood-brain barrier are valsartan, telmisartan and candesartan, depending on the lipophilic properties of each drug.[1,3,6,7]

a. Telmisartan

Telmisartan has been shown to have beneficial safety and tolerability, either as a single therapy or in combination. Telmisartan releases angiotensin II from its binding site at AT1 receptor and selectively binds to the AT1 receptor. This bond is long-term. Based on the degree of affinity to receptors Telmisartan > olmesartan > candesartan > valsartan ≥ losartan. Compared to its class of drugs, telmisartan has the longest plasma half-life and the highest lipophilic properties. The peak plasma time (Tmax) of telmisartan is 0.5-1 hour after oral administration, and the half-life in plasma is ~24 hours. Telmisartan's bioavailability is low <50%, and binding to proteins is high (>90%), generally albumin and alpha-1 glycoprotein acid. Telmisartan can inhibit p-glycoprotein which can affect penetration into the brain.[3,5–7,9]

Telmisartan does not interact with drugs that inhibit or are metabolized by the enzyme CYP, except CYP2C19. Drugs that have been reported to interact with telmisartan are digoxin and ramipril. Telmisartan can improve memory deficits in type 1 diabetic rats because it affects amyloidosis in the brain. In Alzheimer's cases, telmisartan was reported to decrease the amyloid-β ratio of 42/amyloid-β 40 by increasing amyloid-β 40, a nonpathogenic form of amyloid-β and inhibiting the neurotoxic effects and plaque formation by amyloid-β 42.[1,5–7,9,11,13]

b. Olmesartan

Olmesartan medoxomil, given in the form of a prodrug, is rapidly converted into active metabolites upon absorption in the gastrointestinal tract. The most common side effects are headaches, upper respiratory infections and influenza-like symptoms. Olmesartan is not metabolized by the cytochrome system p-450.[3,5]

Olmesartan can increase adiponectin levels and improve insulin sensitivity in diabetic nephropathy patients. Adiponectin is neuroprotective against focal cerebral ischemia. Adiponectin suppresses the release of interleukin 6 from brain endothelial cells and other proinflammatory cytokines, whereas insulin can cross the blood-brain barrier and compete with amyloid-β for enzymes that degrade insulin in the brain. This leads to decreased degradation and accumulation of amyloid-β. .[3,6,9]

c. Candesartan

Candesartan cilexetil is a prodrug that will be converted rapidly into the active drug candesartan by hydrolysis of esters during the absorption process in the gastrointestinal tract. Candesartan binds to AT1 receptors are strong and slow to break down from receptors. Li et al. conducted experiments on Sprague-Dawley rats that in the POCD (postoperative cognitive dysfunction) model found that animals given candesartan prophylaxis for 14 days could cross the morris water maze test better, which means they had a better cognitive function, compared to the control group. This neuroprotective effect is the result of improved blood-brain barrier function and decreased neuroinflammatory signaling (inhibiting the NF-kB pathway, proinflammatory cytokines IL-1β and TNF-α, COX-2). Candesartan administration can decrease the permeability of the blood-brain

barrier, increase the permeability of the transcellular and paracellular blood-brain barrier associated with cognitive function deficits after surgery. Candesartan can normalize glutamate in mouse neuron cultures injured by high concentrations of exocytotic glutamate. [3,6,13,14]

d. Losartan

Studies in rats indicate that losartan does not penetrate the blood-brain barrier. Losartan may interact with the drugs cimetidine, phenobarbital, rifampicin, fluconazole, fluvastatin, bucolome and phenytoin. This interaction affects the metabolism of one of the drugs. Losartan is a prodrug that gets activated in the liver into 2 active metabolites, which act on AT1 receptors and other metabolites useful for producing other additional effects such as decreased oxidative stress and return of DM-induced mitochondrial dysfunction. Losartan was able to decrease amyloid plaque and inflammation in a transgenic animal model of APP/S1 with Alzheimer's.[6,11]

e. Valsartan

Valsartan is a potent and specific ang II receptor antagonist. Increased plasma Ang II levels due to AT1 receptor inhibition can stimulate unobstructed AT2 receptors.[3,6]

f. Irbesartan

Almost all ARBs have low oral bioavailability, usually lower than 50%, except Irbesartan which has a bioavailability of 70%. Irbesartan inhibits Ang-induced apoptosis in human endothelial progenitor cells via pathways involving c-Jun N terminal kinase and p38 mitogen-activated protein kinase, lowers Bcl-2, and increases Bax and caspase 3 activations. Irbesartan also completely inhibits the formation of ROS generation-induced advanced glycation end-products (AGE) and gene expression of vascular cell adhesion molecule-VCAM-1. [3,6,7]

g. Azilsartan

Azilsartan is a prodrug that will be hydrolyzed rapidly into the active group of azilsartan. This drug is potent and selectively antagonistic to the AT1 receptor. Azilsartan has advantages in terms of potency, protective effect on the heart, and stability in keeping blood pressure under control. Liu et al found azilsartan can protect endothelial cells of rodent brain cells and mice by maintaining the mitochondrial function, p-eNOS-mediated anti-inflammatory activity, and activation of the PPAR-γ pathway. Azilsartan can increase mitochondrial membrane potential, decrease cytochrome c release, maintain ATP synthesis, and inhibit mitochondrial swelling. Azilsartan will increase eNOS activation. eNOS (endothelial nitrit oxide synthase) is an enzyme that is constitutively expressed in endothelial cells and the NO produced from this eNOS is endogenous protective against neurological conditions. PPAR-γ activation is known to induce anti-inflammatory and antioxidant effects on various organs, including the brain. Azilsartan is well tolerated, the most commonly encountered side effects are headache and diarrhea.[3,5,11]

h. Eprosartan

The likelihood of serious side effects is low and there have been no reports of clinical drug interactions. Treatment with eprosartan for one year is associated with a gradual decrease in blood pressure and stabilization or improvement of MMSE (mini-mental state examination score) scores.[6]

5. Conclusion

RAS plays a role in the regulation of blood pressure and electrolyte-body fluid homeostasis. RAS receptors consist of AT1 receptors and AT2 receptors. The brain contains all the components of the renin-angiotensin system. ARB drugs work by inhibiting the effects of angiotensin II on specific AT1 receptors, and indirectly activating AT2 receptors. The presence of RAS in the brain raises suspicions, ARBs also have neuroprotective effects. The pleiotropic effects of ARBs protect neurons by decreasing inflammatory processes and apoptosis, protecting the blood-brain barrier by maintaining blood flow to the brain, resulting in the integrity of the blood-brain barrier. Several preclinical trial studies have shown the benefits of ARBs in correcting brain disorders. However, controlled clinical trials studying the brain-protective efficacy of each ARB have never been conducted.

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