Chapter

Role of the Renin-Angiotensin-Aldosterone System in Various Disease Processes: An Overview

Volkan Gelen, Abdulsamed Kükürt and Emin Şengül

Abstract

The renin-angiotensin-aldosterone system is a physiological system that plays an important role in the regulation of blood pressure and body water-electrolyte balance, in which the kidney, liver and lungs play a role in its activation. This system comes into play in various diseases such as the cardiovascular, renal, pulmonary and nervous system where blood pressure and fluid-electrolyte balance may change. The purpose of this study, which is presented in line with this information, is to explain the working principle of this system, how this system is activated, how it comes into play in the mentioned diseases, and what kind of results occur.

Keywords: Renin, angiotensin, aldosterone, ACE2, hypertension, pulmonary diseases, renal diseases, neurodegenerative diseases, AngII, Covid-19

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) is a powerful system that regulates fluid-electrolyte balance and systemic blood pressure. First, it has been stated that it is a hormonal and peptidergic endocrine system that regulates blood pressure and fluid-electrolyte balance [1, 2]. Until recently, RAAS was known only as an endocrine system that regulates blood pressure and fluid-electrolyte balance, but now it is noted that this system is not only found in circulation but also locally in organ systems, and also has autocrine-paracrine functions [3].

There are some components of RAAS responsible for these effects. One of these components, renin, is synthesised as prorenin from the juxtaglomerular apparatus, which is also found in kidney efferent arterioles. The protein is converted to active renin, stored in secretory granules and released into the circulation when necessary [4]. The release of renin, a proteolytic enzyme, is triggered by many physiological stimuli, including prostacyclins (PGI2), such as stimulation of macula densa in the distal tubule with low Na + concentration, reduction of arterial pressure, renal sympathetic nerve activation and stimulation of β1-receptors [5]. Circulating renin provides the formation of Angiotensin I (AngI) from angiotensinogen, most of which is synthesised from the liver [6]. AngI is converted to Angiotensin II (AngII) by Angiotensin-converting enzyme (ACE), a membrane-bound metalloproteinase found in high amounts on pulmonary vascular endothelial cell surfaces (**Figure 1**) [5, 7].
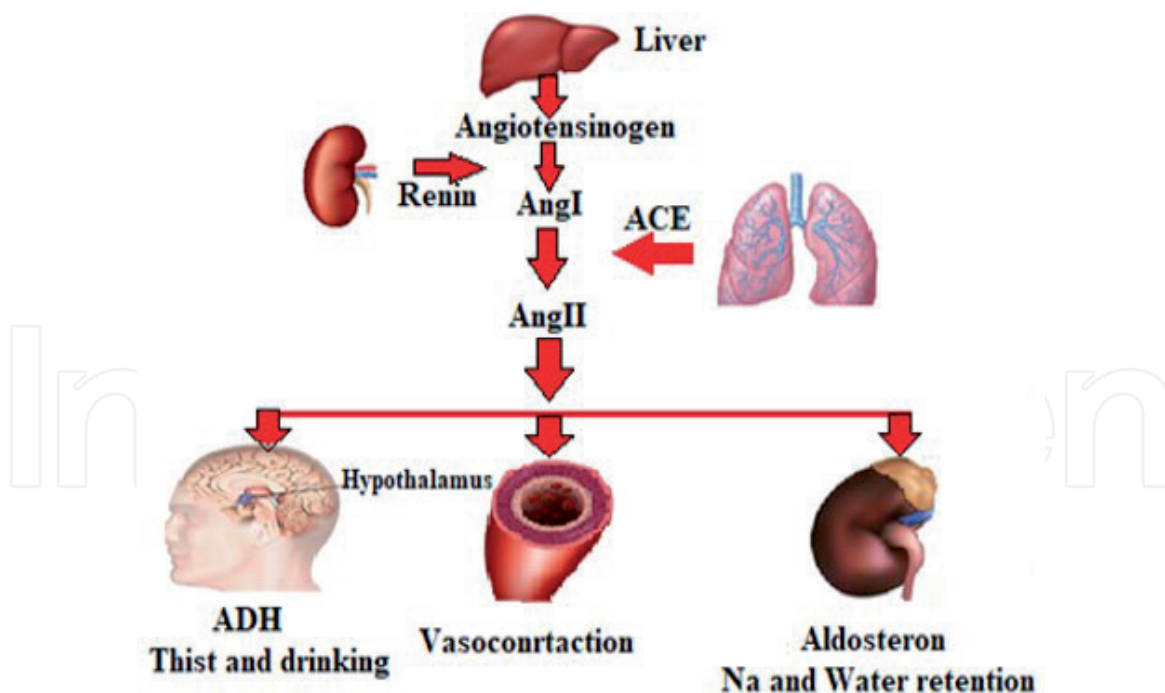
Figure 1.
Renin-angiotensin-aldosterone system and effects.

ACE, a member of the zinc metallopeptidase class, had two main roles in metabolism. It takes part in the RAAS system and the kinin-kallikrein system (KKS). Another task is to inactivate substance P and neurokines [8, 9]. ACE has two forms in endothelial and epithelial cells and male spermatid. Its form in endothelial and epithelial cells is called "somatic form" (sACE), and the form found in spermatids is called "germinal form" (gACE) [10]. The primary structure of these two forms is different from each other. While sACE has two active sites with different catalytic properties, gACE has only one active [11]. ACE has another mammalian homologue named angiotensin-converting enzyme 2 (ACE2) [12]. Although ACE2 has carboxypeptidase activity like ACE, it cleaves an amino acid unlike ACE and its most important substrates are AngI and AngII [13].

In the body, AngII has many roles such as increasing blood pressure by direct contraction of vascular smooth muscles, increasing myocardial contractility, water and salt retention by stimulating aldosterone release from the adrenals, stimulation of catecholamine release from sympathetic nerve endings, cell growth and proliferation [14, 15]. It turns out that AngII can be generated locally in many tissues, including the brain, independent of circulating components [16]. AngII acts by binding to receptors in the protein structure on the plasma membranes of different tissues. These receptors are termed AngII type 1 (AT1R) and AngII type 2 (AT2R) receptors [17]. Changes in the balance of RAAS have been reported to have direct or indirect effects with cardiovascular system diseases, lung diseases, nervous system diseases and kidney diseases. Therefore, this section describes the mechanism of action of RAAS and the relationship of RAAS components with these diseases.

2. The role of RAAS in cardiovascular disease

2.1 Heart failure and myocardial infarction

Ang II has a role in a variety of cardiac dysfunctions, including hypertrophy, arrhythmia, and ventricular dysfunction [18, 19]. Inability to pump enough blood

to the body due to insufficient heart functions due to various reasons is known as heart failure. When looking at the role of RAAS in the case of heart failure, RAAS activation can occur when hypertrophy occurs in the heart muscle cells. This causes fluid retention in the body and peripheral vasoconstriction, resulting in cardiac overload and heart failure [20]. RAAS activation increases in heart rate and contractility, thus reducing coronary blood flow [21]. Experimental studies have shown that plasma renin activity increases in acute heart failure. Also, it was determined that plasma renin activity was normal in the compensated phase of chronic heart failure, and this shows that RAAS is associated with heart failure [22]. It has also been determined that when myocardial cells are exposed to excessive AngII and aldosterone, fibrosis is formed. This again shows that RAAS plays an important role in myocardial heart disease. It was determined that AT-1 receptor expression affected by AngII decreased in decompensated heart failure, while AT-2 receptors remained unchanged [23]. It has also been determined that ACE inhibitors play an important role in heart failure. It has been reported that ACE inhibitors are beneficial, especially in patients with left ventricular failure, and that death rates are reduced [24]. These findings are an important indicator that renin-angiotensin inhibition is crucial to improving cardiac dysfunction. When the relationship of RAAS with myocardial infarction is examined, it has been determined that ACE2 RNA expression increases in the case of myocardial infarction [25]. In another study, it was shown that ACE2 expression increased in the case of myocardial injury induced by ischemia–reperfusion in rats and this increase attenuated myocardial damage [26].

2.2 Hypertension

It has been determined that the plasma renin level changes in the case of hypertension. Plasma renin levels are not proportional to blood pressure, and it has been reported that plasma renin levels are low in some patients, normal in others and high in others. One of the reasons for the change in the renin level is that it is primarily caused by ischemia that develops in the nephrons. In this case, renin levels released from ischemic nephrons increase at different levels, resulting in normal or high plasma renin levels. The renin released from ischemic nephrons passes into the circulation leading to the formation of AngII [17, 27]. As a result, hypertension occurs with increased vasoconstriction and sodium retention in nephrons. The reason why plasma renin level is normal in some hypertensive patients is that aldosterone is not synthesised in response to sodium restriction. Also, it has been stated that resistance to renin and AngII is formed in the vessels and therefore they can increase blood pressure even at low levels. Besides, independent of RAAS in circulating blood, it has been determined that Ang II production by serine protein kinase activity is independent of ACE activity in the heart, brain, adrenal cortex and blood vessels [28]. Also, AngII contributes to hypertension [29]. When looking at the relationship between salt intake and RAAS, it is seen that high salt intake suppresses RAAS, while low salt intake stimulates AngII release [30]. Studies have determined that smooth muscle cells are also critical in the regulation of AngII-mediated blood pressure. A study in mice found that 22α protein deficiency in smooth muscle reduces hypertension that can occur with AngII [31]. This is an indication that the RAAS system plays an important role in hypertension.

2.3 Atherosclerosis

AngII has been determined to induce endothelial dysfunction and increase oxidative stress in the endothelium by stimulating the production of reactive oxygen

species (ROS) such as superoxide anions (O2−) derived from nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase). This is especially the result of endothelial AT1R stimulation that interacts with the Nox5/Ca2 + calmodulin binding site, which will increase Ca + concentration in the endothelial cell [32, 33]. Nox5 is a member of the NADPH oxidase family and plays an important role in the development of atherosclerosis, inflammation, and oxidative stress [33, 34]. It also plays a role in the adhesion of mononuclear cells to the arterial endothelium and recruitment of mononuclear cells by stimulating the increase in CAM expression of TNF-α, which is released as a result of stimulation of AT1R with AngII, in combination with IL-6 [35]. One study reported that AngII induced monocyte chemotactic protein-derived protein expression (MCPIP1) via an AMPK/p38 MAPK-dependent pathway [36]. Increased MCPIP1 expression contributes to atherosclerotic plaque formation by triggering apoptosis in macrophages [37]. Another thing related to the formation of atherosclerosis is that AngII induces the expression of a multi-functional protein found in macrophages, endothelial cells, smooth muscle cells (SMCs), and epithelial cells called osteopontin. Osteopontin plays an important role in the development and development of atherosclerosis [38]. The cell membrane has a transmembrane glycoprotein called LOX. LOX acts as a receptor for oxidised LDL (oxLDL). It increases the expression of AngII LOX-1 gene. Binding of oxLDL to LOX-1 in the endothelium causes an increase in leukocyte adhesion molecules, activates apoptosis pathways, increases ROS and induces endothelial dysfunction. This situation contributes to the development of atherosclerosis. Also, oxLDL increases the formation of ACE, which induces the formation of AngII (**Figure 2**). This increases LOX-1 expression, which positively regulates the expression of AT1R, and contributes to a self-sustaining pro-atherogenic cycle [39]. Thus, it has been determined that ACE and ATR1 inhibitors prevent the development of atherosclerosis.

2.4 Vascular inflammation

RAAS plays an important role in shaping vascular inflammation. Vascular inflammation causes endothelial dysfunction. This dysfunction causes tissue damage. Endothelial dysfunction also results in the accumulation of inflammatory cells in the area. This situation triggers atherosclerosis. Also, studies have shown that
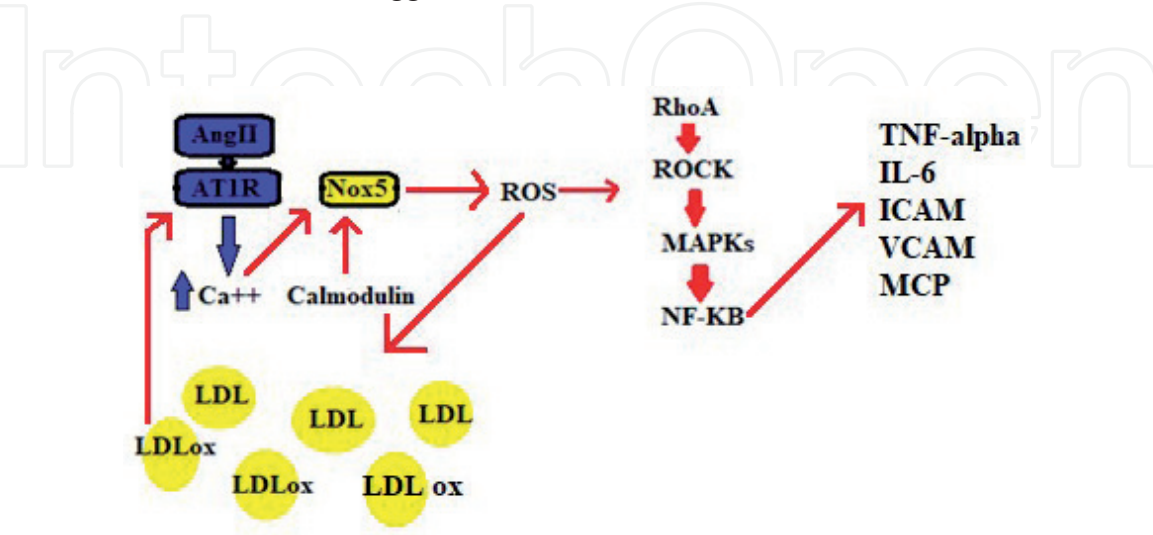

Figure 2.
Mechanism of AngII-mediated atherosclerosis formation. Involvement of Ang-II, ACE2, and Ang-1–7 in atherogenic pathways. The Ang-II binding into AT1R can activate Nox5 through a calcium/calmodulin-dependent pathway.

AngII-mediated inflammation and hypertension and atherosclerosis develop [40]. In another study, it was determined that AngII administration in human vascular smooth muscle cells increased NF-KB activation, thus increasing IL-6, MCP-1 and TNF-expression [41]. Again, although it is a vasoconstrictor, AngII was determined to induce endothelial damage by inhibiting endothelial cell regeneration. AngII has been reported to act as a second messenger to activate intracellular signalling pathways such as mitogen-activated protein kinase (MAPK) and protein kinase Akt/protein kinase B (Akt/PKB), pathways that mediate cell proliferation and apoptosis, and thus vascular dysfunction [42]. AngII is also stated to be a potent pro-oxidant. Ang II induces the production of superoxide anions and activates NADH/NADPH signalling [43]. AngII lowers nitric oxide (NO) levels and activates redox-sensitive genes, particularly cytokines and adhesion molecules [44]. Ang II is also a profibrotic factor. Chronic AngII administration in mice has been shown to cause an increase in blood pressure, infiltration of inflammatory cells into the myocardium and cardiac fibrosis [45]. Another factor that provides the proinflammatory and profibrinolytic effect of RAAS in vessels is aldosterone [46]. Aldosterone affects insulin resistance and the development of atherosclerosis. In vascular smooth muscle cells, aldosterone alters insulin signalling, increases insulin-like growth factor-1 expression.

2.5 Oxidative stress

Oxidative stress is defined as the disproportion between the presence of anti-oxidants and free radicals or prooxidants in a biological system. ROS and reactive nitrogen species (RNTs) are by-products of a variety of cellular processes, including aerobic metabolism [47–51]. These by-products cause damage to various tissues [52–73]. RAAS has a direct relationship with oxidative stress that may occur in the cardiovascular system. It has been determined that chronic administration of aldosterone, one of the components of RAAS, causes oxidative stress in the rat aorta [74]. AngII represents one of the major vasoactive peptides involved in the regulation and activation of NADPH oxidase. Ang II stimulates the activation of NADPH oxidase, increases the expression of NADPH oxidase subunits, and induces ROS formation in vascular smooth muscle cells, endothelial cells and fibroblasts. ACE2 shows an effect of reducing oxidative stress by inhibition of ROS synthesis by reducing AngII to Ang 1–7. Ang 1–7 therapy can have a curative effect on vascular disease models. It is reported that solutions that can increase Ang 1–7 levels may be beneficial to alleviate endothelial dysfunction [75]. This is supported by studies showing that overexpression of ACE2 leads to attenuating the effects of hypertension in animal models [76, 77]. It supports the argument that hypertension is a side effect directly related to oxidative stress, thus overexpression of ACE2 leads to a reduction of oxidative stress in a biological system [78].

3. The role of RAAS in renal diseases

3.1 Proteinuria

RAAS plays an important role in the pathogenesis of many kidney diseases characterised by proteinuria. In a study, it was stated that AngII induces the formation of proteinuria. It has also been determined that AngII stimulates the formation of TGF-1 in various kidney cells [79]. TGF-1 has been found to impair autoregulation by afferent arterioles [80]. Vasoconstriction occurs after increased arterial

pressure in afferent arterioles. In case of impaired autoregulation in the presence of TGF-1, especially systemic hypertension occurs, an increase in transcapillary pressure occurs. Thus, AngII increases capillary filtration pressure by causing efferent vasoconstriction and TGF-1-mediated impaired afferent arteriole auto-regulation. Also, AngII has been found to have a direct effect on the integrity of the filtration barrier. Again, AngII has been shown to reduce the synthesis of negatively charged proteoglycans and additionally suppress nephrin synthesis [81]. It has been observed that this situation causes apoptosis in podocytes. Vascular endothelial growth factor (VEGF) has been identified to be an important factor in increasing the permeability of the filtration barrier in the kidneys [82]. It has been determined to stimulate VEGF expression via the AngII, AT1 and AT 2 receptors. It is thought that the increase in VEGF expression via AT2 receptors may be mediated by an increase in hypoxia-inducible factor 1. Also, VEGF and TGF-1 mediate the AngII-mediated synthesis of the 3rd chain of collagen type IV, which is a component of the glomerular basement membrane [83, 84]. As a result, it is seen that AngII causes proteinuria by causing changes in hemodynamic and non-hemodynamic mecha-nisms. AngII stimulates albumin reabsorption in proximal tubule cells through AT2 receptor-mediated protein kinase B activation [85]. Albumin uptake induces a selection of proinflammatory and profibrogenic cytokines such as monocyte che-moattractant protein-1, IL-8, endothelin, and TGF-1 [86]. This situation stimulates the migration of cells into the interstitium. Ultimately it causes inflammation in the interstitial area.

3.2 Fibrosis

In a study, ECM proteins induce type I procollagen and mRNA encoding fibro-nectin in cultured mesangial cells of AngII, and also stimulates the synthesis of type I collagen types 1 and 3 in cultured proximal tubular cells [79]. It has been determined that the stimulatory effect of AngII on collagen expression is dependent on TGF-1 expression. As a result of the studies, it has been reported that AngII stimulates the proliferation of cultured renal fibroblasts and increases mRNA expression of TGF-β1, fibronectin and type I collagen. It has also been observed that renin increases TGF-1 expression by stimulating a particular receptor in cultured mesangial cells [87]. These findings suggest that increased renin as a result of ACE inhibitor therapy may directly contribute to renal fibrosis through increased TGF-1 despite AngII blockade. It was also determined that AngII increased connective tissue growth factor (CTGF) in kidney tissue. CTGF is a fibrinolytic mediator and is also stimulated by TGF-β. However, AngII also stimulates CTGF synthesis independently of TGF-β [88]. These findings suggest that increased renin as a result of ACE inhibitor therapy may directly contribute to renal fibrosis through increased TGF-1 despite AngII blockade. It was also determined that AngII increased connec-tive tissue growth factor (CTGF) in kidney tissue. CTGF is a fibrinolytic mediator and is also stimulated by TGF-β. However, AngII also stimulates CTGF synthesis independently of TGF-β [89]. Studies have shown that more than one-third of local fibroblasts in renal interstitial fibrosis originate from tubular epithelial cells through a process called epithelial to mesenchymal transition (EMT). Again, AngII can be effective on EMT [90].

3.3 Inflammation

Studies have shown that AngII activates the proinflammatory transcription factor NF-KB via AT1 and AT2 [91]. It has also been stated that it can stimulate

NF-KB in AngIII and AngIV [86]. It has been determined that Rho-kinase plays a role in AngII mediated NF-KB activation. Also, AngII stimulates the transcription factor Ets. This factor regulates vascular inflammation by the transport of T cells and macrophages to the vascular wall. AngII has been reported to increase the level of Toll-like 4 receptors that bind LPS on mesangial cells. It has been observed that this receptor has an increasing effect on NF-KB activation [92]. The penetration of inflammatory cells into the glomerulus as well as the tubulointerstitium plays an important role in the progression of chronic kidney disease. Also, AngII induces the adhesion of circulating immune cells to capillaries by stimulating the increase of adhesion molecules such as vascular cellular adhesion molecule-1, intraclular adhesion molecule-1 and integrins. This situation shows the relationship of AngII with renal inflammation. It has also been determined that AngII has a stimulating effect on lymphocyte production [86, 93].

3.4 Chronic kidney disease (CKD)

Studies explaining the relation of RAAS with CKD were made in the 1980s and important data were obtained in these studies [94]. AngII has emerged as a central mediator of kidney damage because it can induce glomerular capillary hypertension that damages endothelial, glomerular epithelial cells, and mesangial cells [94, 95]. Also, AngII/aldosterone has non-haemodynamic effects that are important in the pathogenesis of CKD, such as inflammation, fibrosis, ROS production, and activation of pathways associated with endothelial dysfunction [94]. One of the most common causes of CKD is diabetic nephropathy. RAAS has an important role in diabetic nephropathy. Plasma renin activity is lower than normal in patients with diabetes [96]. However, intra-renal RAAS activity is high [97, 98]. This is an indication that diabetic nephropathy has one of the most important roles in the formation of CKD.
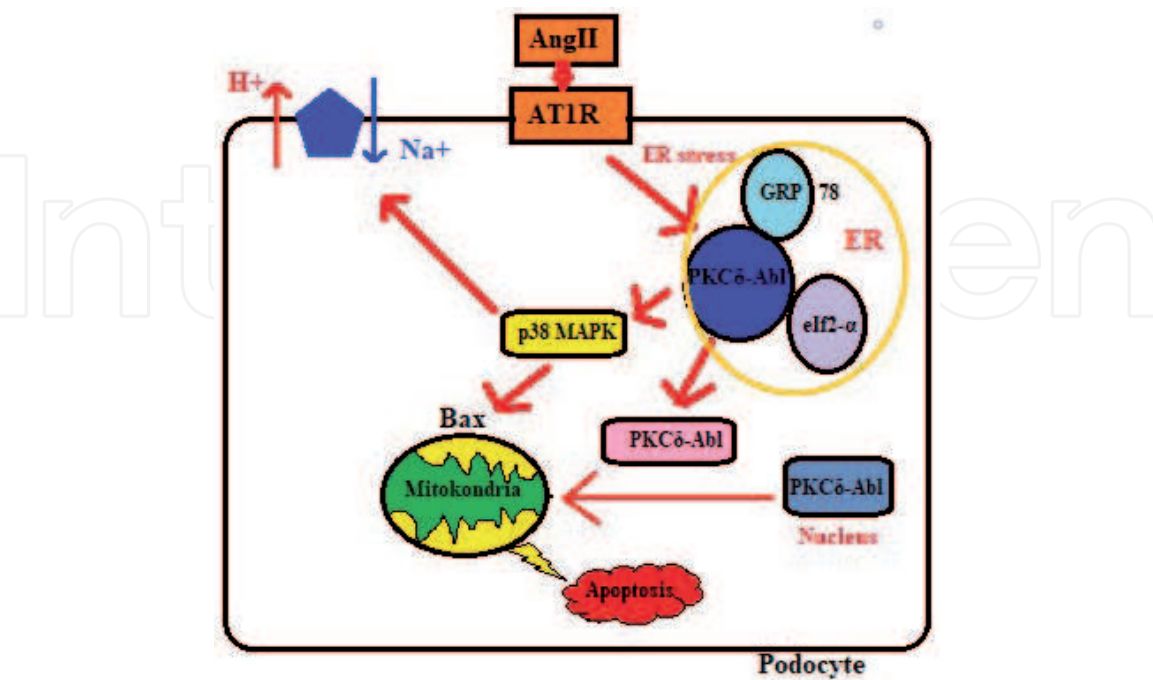

Figure 3.
Mechanism of AngII-mediated apoptosis formation in the podocyte. AT1R signalling induces ER stress through increased GRP 78 and p-elf2α expression and PKC-δ phosphorylation. p38 MAPK and PKC-δ activation lead to increased Bax expression and enhanced NHE1 activity, triggering cellular apoptosis.

3.5 Apoptosis

Studies show that the RAAS system is associated with renal hypertrophy and apoptosis. It has been determined that AngII, one of the components of RAAS, induces apoptosis in vivo and in vitro conditions [99]. It has been reported that AT1 and AT2 receptors are involved in these effects. Studies have reported that Ang II plays an important role in tubular cells and podocytes in (Endoplasmic reticulum) ER stress-induced renal apoptosis, especially in diabetic nephropathy [100]. It has been shown that Ang II can induce podocyte ER stress via the PERK-eIf2-α-ATF4 axis and the PI3-kinase pathway [101]. Another study found an AT1R-mediated increase in glomerular GRP 78 in rats chronically treated with AngII. These data support the relationship between the AngII/AT1R signal and ER stress on podocyte damage. In the same study, Ang II treatment was reported to induce p38 MAPK-dependent apoptosis in podocytes associated with Bax protein activation. In addition, Na+/H+ exchanger isoform 1 (NHE1) activity increases. As a result, it triggers cellular apoptosis (**Figure 3**), [102].

4. The role of RAAS in lung diseases

4.1 Acute lung injury and pneumonia

As a result of RAAS activation, inflammation [103] and vascular permeability increase [104] due to Ang II stimulation of AT1 receptor and thus severe acute lung damage occurs [105, 106]. In mice, administration of losartan prevents acute lung injury caused by Ang II and decreases AT1R expression [107, 108]. Pneumonia is associated with RAAS, especially in influenza-induced types of pneumonia RAAS system plays a very important role. In patients with pneumonia, the use of RAAS inhibitors reduces the mortality rate and the likelihood of intubation [109]. As with other viral types of pneumonia, children infected with the Respiratory syncytial virus (RSV) tend to have higher Ang II levels than healthy children [110]. The benefit of recombinant ACE2 treatment on RSV infection has been demonstrated in a preclinical mouse model in animal experiments [111]. H7N9 and H5N1 influenza reduce the level of ACE2, increase the level of Ang II, and thus cause lung damage via the AT1 receptor [112]. In H5N1 and H7N9 mouse models, treatment with losartan results in a decrease in IL-6 level and lung oedema, thus preventing lung damage [113]. It was concluded that losartan prevents lung damage by inhibiting RAAS activity.

4.2 SARS-CoV viral infection

The Spike protein [S protein] on the SARS-CoV Virus surface attaches to the ACE2 receptor and enters the body in this way. Moreover, ACE2 improves the efficiency of SARS-CoV replication [114]. Transmembrane protease serine 2 (TMPRSS2) can degrade ACE2 and S protein for membrane fusion and the entry of SARS-CoV into cells. Therefore, the concentration of ACE2 in the membrane decreases, but the number of cells infected with SARS-CoV with cessation increases [115]. Ang-II level increases in lung tissue of mice infected with SARS-CoV. Also, the use of angiotensin receptor blockers in these animals significantly reduces pulmonary oedema. This indicates that lung failure caused by SARS-CoV is caused by an increase in Ang-II level and overactivation of the AT1 receptor [116]. Increased ACE level and decreased ACE2 levels in SARS patients cause increased Ang II level

and AT1 receptor expression, which accelerates lung damage and can lead to death [117]. Also, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), caspase 3 (CASP3), caspase 9 (CASP9) and fibroblast growth factor-7 (FGF-7) increase in the lung tissue of these patients [118].

4.3 SARS-CoV-2 viral infection

SARS-CoV-2 (Covid-19) Similar to SARS-CoV, the S protein uses the ACE2 cellular membrane for input and uses TMPRSS2 for S protein preparation to facilitate the fusion of viral and cellular membranes [119–121]. Compared to other coronaviruses, the affinity of S protein to ACE2 is higher in SARS-CoV and SARS-CoV-2. Looking at the distribution of ACE2 receptors in the body, it is found on the endothelial cells and smooth muscle cells of organs and tissues, including the oral and nasal mucosa, lung, small intestine, kidney, heart and blood vessels. The widespread distribution of ACE2 receptors in the body is an indicator of multi-organ failure in COVID-19 patients [122–124]. SARS-CoV-2 infection causes RAAS disorders and systemic inflammatory response. The plasma Ang II level of COVID-19 patients is significantly higher than that of healthy individuals. This condition is linearly related to viral load and lung injury [125]. A clinical study has shown that cytokine storm syndrome (CSS) occurs in patients with COVID-19 and severe pneumonia. Also, it showed that some cases can progress rapidly to Acute respiratory distress syndrome (ARDS) and even to multiple organ failure [126]. Inflammatory cytokines and chemokines are synthesised in Covid-19 patients, including IL-6, IL-2, IL-1β, IL-8, IL-17, IFN-γ, TNF-α and monocyte chemoattractant protein-1 (MCP-1) (**Figure 4**). Among them, however, IL-6 in particular plays a key role in triggering the inflammatory response, increasing the mortality rate in patients [125]. In Covid-19 infection, after the virus binds to ACE2 on the cell surface, Ang II cannot convert to Ang1–7, and thus more and more binding occurs to AT1 receptors. This situation causes an imbalance in the ACE/ Ang II/AT1R axis. As a result, the pulmonary endothelium and epithelial cells are damaged by stimulating inflammatory signalling pathways, resulting in an increase in the permeability of pulmonary capillaries [127].
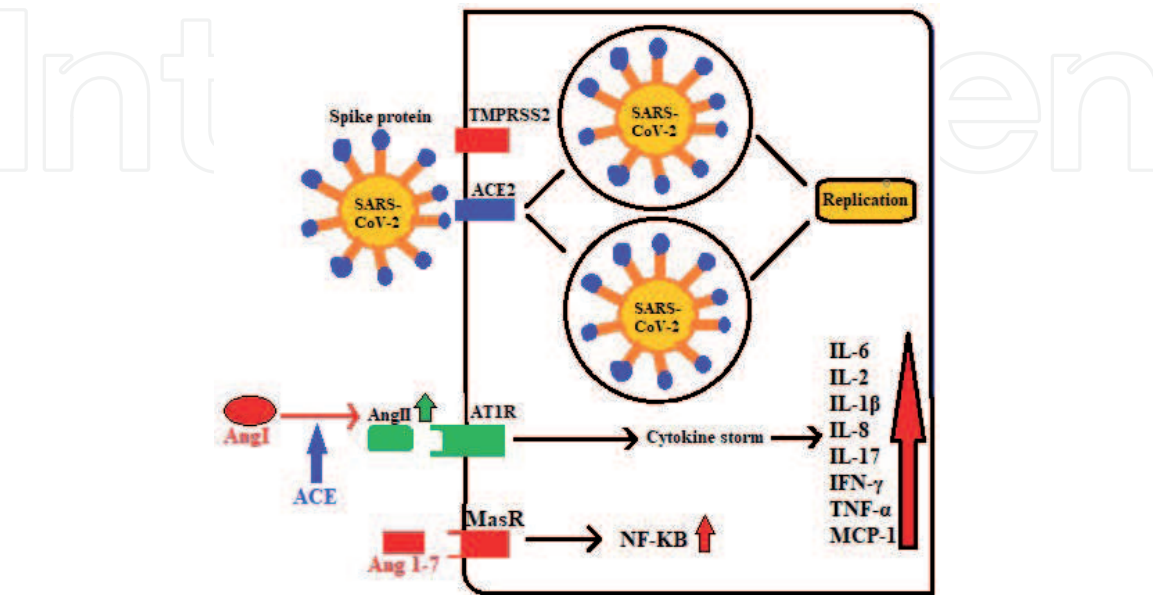

Figure 4.
Effects of the renin-angiotensin system during SARS-CoV-2 infection.

5. The role of RAAS in some neurological disorders

Brain RAAS irregularity may contribute to neurodegeneration due to neuroinflammation, oxidative stress and pathophysiological changes due to ageing. Several studies have reported that irregular RAAS plays a key role in numerous degenerative diseases of the brain, including Alzheimer's, Parkinson's disease, Huntington's disease, dementia, amyotrophic lateral sclerosis, Multiple sclerosis, Traumatic brain injury, and Stroke [128–130].

5.1 Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterised by impaired daily functions and behaviour, especially memory [131]. The most important change in AD neuropathology is Aβ-centred senile amyloid plaques formed in the hippocampus, amygdala and cortex. Neurovascular disorders and chronic neurodegeneration occur in the surrounding brain tissues and vessels as a result of the toxic effects of these plaques [132]. Besides these plaque formations; Neurofibrillary tangles, oxidative stress in cell membranes and organelles, inflammation, gliosis, excitotoxicity due to excessive intracellular Ca + 2 increase and neuron death by many mechanisms that trigger each other such as disruption in membrane cation channels are encountered [133, 134]. The amyloid-beta (Aβ) peptide triggers O2 radical production in endothelial cells and induces oxidative and peroxidative reactions, causing cell death. As an example of these reactions; the oxidative reaction catalysed by the combination of amyloid plaques with heavy metal ions and lipid membrane peroxidation by various mechanisms can be given. It has been observed that the increased ROS activity via Aβ in tissue taken from the hippocampus caused synaptic disruption and cell death as a result of increased Ca + 2 increase with N-methyl-D-aspartate (NMDA) channel activation. Besides, mitochondria dysfunction is an important point in AD pathology. In biopsy studies, it was found that mitochondria shrank and protein and DNA dispersed into the cytoplasm [135, 136].

One of the brain RAAS products, the Ang- (1–7) peptide is a Mas receptor [MASR] agonist [137]. MASRs are abundant in memory-related areas of the brain and accelerate hippocampal long-term potentiation (LTP) together with Ang- (1–7). Also, it is known that the neuroinflammatory effects of Ang II, another RAAS product, contribute to cognitive disorders. Reversing the biological effects of Ang II with the anti-inflammatory, anti-fibrotic, vasodilator and anti-proliferative biological effects of Ang- (1–7); supports memory and learning [138]. In brain tissue studies in AD, it has been shown that the expression and activity of ACE, the metabolic enzyme of Ang-II, changes significantly in certain regions of the brain, including the frontal cortex and hippocampus. It has been reported that when centrally acting ACE inhibitors are used, they have reduced cognitive decline and have memory-enhancing effects [139, 140]. ACE2 activity decreases in AD pathology [141]. Ang- (1–7) improves memory functions without affecting hippocampal or cortical amyloid peptide storage [142].

Ang II causes oxidative stress through the AT1 receptor [143] and increases superoxide. Thus, it causes neuroinflammation and vascular diseases [144]. As a result, it causes Aβ accumulation due to AD. However, the AT2 receptor signal produces beneficial effect including learning and memory. Angiotensin receptor blockers (ARBs) inhibit AT1R signalling, which shifts the effect of Ang-II towards the beneficial path (AT2R signal) (**Figure 5**) [144].

ACE inhibitors have a protective effect against AD. It shows this effect by suppressing brain-derived neurotrophic factor reduction and TNF-α release.
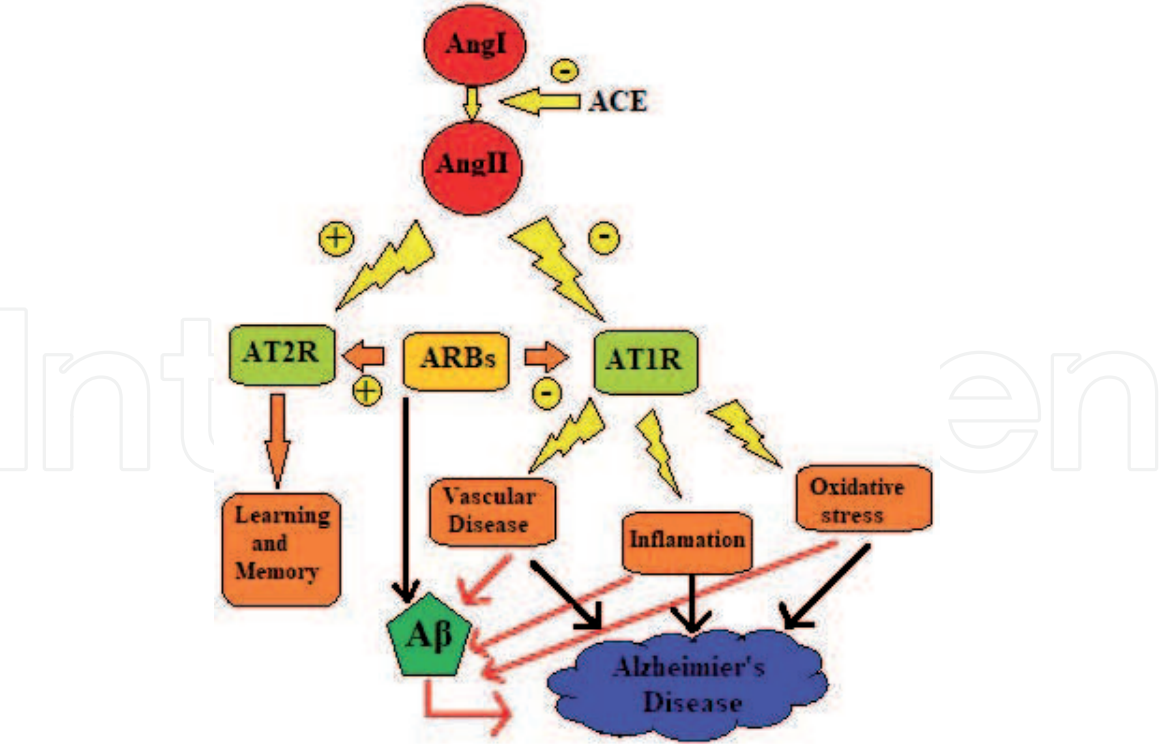
Figure 5.
Effect of AngII on the nervous system. Amyloid plaque (Aβ), angiotensin II (AngII), angiotensin I (AngI), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin (AT), AT2 receptor (AT2R), AT1 receptor (ATR1R).

ACE inhibitors also improve oxidative-nitrosative stress and nitrotyrosine production, which reduces amyloidogenesis and subsequent Aβ accumulation [145, 146]. On the other hand, ACE inhibitor (Captopril) and Angiotensin receptor blockers (Telmisartan, Candesartan, Losartan) ameliorate oxidative stress [147–151]. Telmisartan normalises the decreased thioredoxin (TRX) system in addition to attenuating the expression of the protein (TXNIP) that interacts with thioredoxin. Thus, it reduces the formation of endogenous ROS [149]. Similarly, telmisartan reduces improved glycation end products and 4-hydroxynonenal, which are markers of oxidative stress and are associated with Neurodegeneration [150]. Candesartan lowers the level of free radicals in the brain by decreasing malondialdehyde and increasing glutathione levels [151].

5.2 Parkinson's disease

Ang II levels are high in the striatum and substantia nigra of Parkinson's disease (PD) patients. Ang II and AT1R trigger apoptosis by activating autophagy in a dopaminergic neuronal cell. These findings suggest that Ang II plays a role in the pathogenesis of PD [152]. In animal models of PD, it has been found that the signalling of AT2Rs is decreased with the loss of function in dopaminergic neurons [153]. Also, ACE and ACE2 were detected in the cerebrospinal fluid of PD patients. ACE levels are decreased in the cerebrospinal fluid of PD patients [154].

5.3 Multiple sclerosis

Multiple sclerosis (MS) is defined as an autoimmune neurodegenerative disease that typically occurs in the third or fourth decade of life [155]. Although the aetiology of the disease is not fully known, both environmental and genetic factors are

thought to play an important role in the development of MS [156]. Blocking angiotensin II production by ACE inhibitors and inhibition of angiotensin II signalling by AT1 receptor blockers suppresses T-helper 17 (Th17) cells [157]. Th17 cells play an important role in the development and relapse of MS [158]. In a study, ACE activity in the blood serum of MS patients was reported to be higher than in healthy controls [159]. In another study, ACE and ACE2 levels were found to be reduced in the cerebrospinal fluid of MS patients [160].

6. Conclusion

As understood, the renin-angiotensin-aldosterone system plays a very important role in regulating the fluid-electrolyte balance and blood pressure in the body. RAAS has receptors in many organs and tissues and can show various effects here. RAAS can be affected by various diseases affecting the cardiovascular, renal, nervous and respiratory systems and plays a major role in the formation of damage that may occur in these systems. Drugs that can affect the components or receptors of RAAS can prevent damage that may occur. The presented study shows the importance of the role of this system in the mentioned diseases. Understanding the role of this system in the mentioned diseases is of great importance in the development of new treatment protocols and new therapeutic agents.

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